

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602

ADMINISTRATIVE DOCUMENTS



Memorandum

Date: May 12, 2003

To: File, NDA 21-106

Through: Robert Temple, M.D., Office Director, ODE I
Richard Pazdur, M.D., Division Director, DODP
David Morse, Ph.D., Pharmacology Supervisor, DODP
Lilliam Rosario, Ph.D., Pharmacology Reviewer, DODP
Sean Bradley, Project Manager, DODP

Subject: NDA 21-602, Bortezomib, Velcade®

From: Jeri El-Hage, Ph.D., ODE I Associate Director for Pharmacology/Toxicology

I have read the Executive and detailed summaries, the labeling sections of the review, and the provided version MPI #3 of the labeling dated May 8, 2003. A minor difference between the division's recommended labeling and the 5/8/03 version was discussed with David Morse via Tcon. This involved an omission of the dose and exposure comparison for the testicular/ovarian findings in the 6-month rat study discussed under the fertility section. While there are some differences in the wording between the labeling recommendations in the pharmacology/toxicology review and the wording in the sponsor's May 8, 2003 version of the labeling, specifically in the non-clinical animal toxicity and overdose sections, the sponsor's wording accurately conveys the information.

The pharmacology reviewer and supervisor have recommended NDA approval contingent upon phase 4 study commitments to investigate _____

_____ Dr. Morse confirmed that the sponsor has agreed to the recommended Phase 4 non-clinical studies. There are no outstanding or unresolved issues at this time.

MEETING MINUTES

MEETING DATE: September 4, 2002

TIME: 3:30 PM, EST

LOCATION: Woodmont Office Complex-2, Conference Room G

IND# _____

Request Submission Date: May 30, 2002

Briefing Document Submission Date: August 13, 2002

DRUG: Velcade™ (bortezomib) for Injection

SPONSOR/APPLICANT: Millennium Pharmaceuticals, Inc.

TYPE of MEETING: End-of-Phase 2

PARTICIPANTS:

FDA

Robert Temple, M.D.	Office Director
Richard Pazdur, M.D.	Division Director
Donna Griebel, M.D.	Medical Team Leader
Peter Bross, M.D.	Medical Reviewer
Greg Frykman, M.D.	Medical Reviewer, Guest
Mark Rothmann, Ph.D.	Statistical Reviewer
William McGuinn, Ph.D.	Pharm/Tox reviewer
Sean Bradley, R.Ph.	Consumer Safety Officer

MILLENNIUM

Nancy Simonian, M.D.	Vice President of Clinical Research
Robert Pietrusko, Pharm.D.	Vice President, Regulatory Affairs
Michael Kauffman, M.D., Ph.D.	Vice President, Medicine
David Schenkein, M.D.	Vice President, Oncology Clinical Development
Dixie Esseltine, M.D.	Senior Director, Clinical Research
Charles Homcy, Ph.D.	President, Research and Development
Julian Adams, Ph.D.	Senior Vice President, Drug Discovery
Tanya Lewis, M.S.	Senior Manager, Regulatory Affairs
Raymond Alexanian, M.D.	Consultant, Medicine
Kenneth Anderson, M.D.	Consultant, Medicine
John Balsler, Ph.D.	Consultant, Biostatistics

MEETING OBJECTIVES: End-of-Phase 2 meeting to explore the pursuance of the registration of PS-341 in multiple myeloma via accelerated approval.

QUESTION for DISCUSSION and DECISIONS REACHED:

Millennium: Data from the first cohort (n=78) of study M34100-025 are summarized in this briefing document. The sponsor intends to complete study M34100-025 by completing data collection and analysis of the second cohort (n=124), and will provide a complete study report to the FDA. Supportive evidence will be provided by one additional Phase 2 study, M34100-024, and three Phase 1 studies.

Does the Agency agree that study M34100-025, supported by the additional studies mentioned above, is sufficient for filing for marketed approval in relapsed and/or refractory multiple myeloma under the accelerated approval regulations detailed in 21CFR314.500, Subpart H?

FDA No. For subpart H approval, a drug must have an effect on a surrogate endpoint that is "reasonably likely, based on epidemiologic, therapeutic, pathologic, physiologic, or other evidence, to predict clinical benefit or on the benefit on a clinical endpoint other than survival or irreversible mortality." In our end of phase 1 meeting on March 9, 2001 as well as in the end of phase 2 meeting on December 7, 2002, we stated that response rates alone would be inadequate to support accelerated approval. In myeloma, response rate has not been demonstrated to correlate with clinical benefit, i.e. survival. For example, Blade, *et. al.* recently reported the results of a large clinical trial comparing MP with high dose conventional therapy (VCMP). "In these trials the response rate significantly correlated with the regimen intensity. However, no significant differences in response duration and survival were found." (Hematol J 2001; 2(4):272-8.)

Subpart H requires that the marketing approval be based on "adequate and well-controlled clinical trials." The data submitted, although promising, appear to be insufficient basis for registration of PS-341 in refractory multiple myeloma. M34100-025 is a single arm study and the study population was small, thus far with only 78 patients reported, and very heterogeneous in terms of prior treatments. Some patients had had 2-3 prior treatments, some had over 7 prior treatments, about half had a PSCT, and 23% had corticosteroids as their most recent treatment. Treatment of non-responders with dexamethasone further confounded results.

Your protocol M34100-039, a randomized, open-label study of PS-341 versus high dose dexamethasone in patients with relapsed or refractory multiple myeloma, is open and accruing patients. This protocol has been reviewed as a Special Protocol Assessment, and we have agreed to the design and primary objective of superiority of time to progression and secondary clinical benefit endpoints of this study. Approval of this drug at this time on the basis of limited data may impede or preclude completion of this randomized trial. Access to Velcade for patients prior to approval may be obtained through additional controlled clinical trials and expanded access programs. We would be happy to work with you in the initiation of an expanded access program.

In conclusion, we recommend that you complete your present randomized study of Velcade vs. Dexamethasone in patients with relapsed or refractory multiple myeloma. We believe that the surrogate endpoint of time-to-progression is more likely to predict meaningful clinical benefit in this randomized trial. In addition, a randomized trial will more accurately characterize the safety of Velcade. In the meantime, patient requirements for Velcade should be met with well designed clinical trials and expanded access programs as mentioned above.

Post Discussion (04SEP02):

FDA: Before filing you NDA, you need to submit the following information in writing and schedule a meeting to discuss the information with the division:

1. Evidence to demonstrate that the results of your phase 2 study are reasonably likely to predict clinical benefit, given the historical lack of correlation between response rates and survival in myeloma trials
2. An update on the status of your randomized trial and an estimation of completion of accrual to show that completion of the randomized trial will not be affected by the filing of the single arm data.
3. More complete characterization of patients in the phase 2 trial to support your assertion that the population is homogeneous and represents an unmet medical need. This should include additional information regarding:
 - their previous treatments (some pts were reported to have undergone >nine prior lines of treatments)
 - response to prior therapies and timing of progression on prior therapies
 - what supporting documentation of progression on prior therapy exists for review?
4. Updated results for the study population (cohort 1 + cohort 2) with attention to complete response rates and response duration. Describe complete response rates with respect to Blade and the old SWOG criteria and clearly distinguish which patients were treated with dexamethasone.
5. Describe how the supportive "clinical benefit" parameters (Ig's and Hgb/transfusion) were systematically ascertained and defined for every patient at baseline and systematically and consistently evaluated on study. If Ig normalization will be proposed as a supportive "clinical benefit" parameter, provide support for clinical relevance of this endpoint. Describe durability of these "clinical benefit" responses.
6. Your proposals regarding expanded access programs.

ACTION ITEMS:

Millennium Pharmaceuticals will respond to the FDA's post-discussion questions and request a meeting with the Agency to further discuss their application prior to submission.

The meeting concluded at 4:40 PM, EST. There were no unresolved issues or discussion points.

Minutes prepared by: _____
Sean Bradley, R.Ph., Project Manager

Concurrence Chair: _____
Peter Bross, M.D., Medical Reviewer

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/s/

Peter Bross
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MEETING MINUTES

MEETING DATE: December 2, 2002

TIME: 3:00 PM, EST

LOCATION: Woodmont Office Complex-2, Conference Room G

IND# _____ Request Submission Date: September 20, 2002
Briefing Document Submission Date: November 13, 2002

DRUG: Velcade™ (bortezomib) for Injection

SPONSOR/APPLICANT: Millennium Pharmaceuticals, Inc.

TYPE of MEETING: Pre-NDA

PARTICIPANTS:

FDA

Robert Temple, M.D.	Office Director
Richard Pazdur, M.D.	Division Director
Grant Williams, M.D.	Deputy Division Director
Ann Farrell, M.D.	Medical Team Leader
Peter Bross, M.D.	Medical Reviewer
Mark Rothmann, Ph.D.	Statistical Reviewer
Sean Bradley, R.Ph.	Consumer Safety Officer

MILLENNIUM

Nancy Simonian, M.D.	Vice President of Clinical Research
Robert Pietrusko, Pharm.D.	Vice President, Regulatory Affairs
David Schenkein, M.D.	Vice President, Oncology Clinical Development
Robert Tepper, Ph.D.	Chief Science Officer and Exec. VP of Discovery
Charles Homcy, Ph.D.	President, Research and Development
Tanya Lewis, M.S.	Senior Manager, Regulatory Affairs
Raymond Alexanian, M.D.	Consultant, Medicine
Kenneth Anderson, M.D.	Consultant, Medicine
John Balser, Ph.D.	Consultant, Biostatistics

MEETING OBJECTIVES: To discuss Cohort 2 data from Clinical Protocol M34100-025 and to reach agreements on the following issues:

1. What response rate is predictive of clinical benefit
2. Does Velcade qualify for accelerated approval

QUESTION for DISCUSSION and DECISIONS REACHED:

Data from the second cohort (n=124) of study M34100-025 are summarized in this briefing document. The first cohort of patients included 78 patients. The sponsor plans to analyze and submit both cohorts in a final study report to the Agency. Supportive evidence will be provided by one additional Phase 2 study, M34100-024, and three Phase 1 studies.

Does the Agency agree that study M34100-025, supported by the additional studies mentioned above, is sufficient for filing for marketing approval in relapsed/refractory multiple myeloma under accelerated approval regulations detailed in 21CFR314.500, Subpart H2

FDA: Fileability will be determined after a preliminary assessment of the submitted NDA confirms the data are reviewable. To be reviewable the data will need to provide all the required components of the NDA described in 21CFR 314.500, and the submitted information must be sufficient to be able to confirm the efficacy and safety claims. In particular for this application, the data must distinguish responses that occurred on PS-341 alone from responses that occurred in combination with dexamethasone.

(See <http://www.fda.gov/cder/guidance/rtf.pdf>)

In order to support approval under the subpart H, you must provide the results of meaningful benefit to patients over existing treatments. For this indication, you will have to show that the population studied is in fact a refractory population. Previous responses to therapy must be documented thoroughly. An explanation should be provided for those responses classified as 'unable to assess.' Information should be provided to allow confirmation of duration of responses.

The heterogenous composition of your study population is likely to hinder interpretation of the efficacy results and therefore the approvability of the NDA. If the clinical evidence is not sufficiently persuasive, we may require the submission of the results of your randomized controlled trial prior to taking regulatory action. We strongly suggest you consider delaying the submission of this NDA until you can include at least some interim response data from your randomized trial.

NDA Review would be expedited by the electronic submission of all study reports and CRF's, in addition to the datasets.

02DEC02-Post Discussion comments:

FDA: From a clinical point-of-view, there currently seem to be no problems with reviewing this application. But the final decision will not be made until the Agency's internal filing meeting for this NDA.

The meeting concluded at 4:15 PM, EST. There were no unresolved issues or discussion points.

Minutes prepared by: _____
Sean Bradley, R.Ph., Project Manager

Concurrence Chair: _____
Peter Bross, M.D., Medical Reviewer

Attachments:

Millennium Pharmaceutical's Slide Presentation

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Peter Bross
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MEETING MINUTES

MEETING DATE: May 8, 2003

LOCATION: WOC II, Conf. Rm. B

HFD-150 Division of Oncology Drug Products

NDA 21-602

DRUG: Velcade (bortezomib)

Proposed Indication: Treatment of relapsed/refractory multiple myeloma

SPONSOR/APPLICANT: Millenium Pharmaceuticals Inc.

TYPE of MEETING: Pre-Approval Safety Conference

REVIEW DIVISION PARTICIPANTS:

Ann Farrell, MD, Acting Medical Team Leader
Robert Kane, MD, Medical Reviewer for Safety
Lillia Talarico, MD, Associate Director

ODS PARTICIPANTS:

Susan Lu, RPh, Safety Evaluator Team Leader
Robert Pratt, Pharm D, Safety Evaluator

Adverse Events To Be Monitored By ODS:

Primary adverse reactions:

- Peripheral neuropathy that is predominantly sensory, although cases of mixed sensory-motor neuropathy have been reported. It's unknown if the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins) will result in combined neuropathic effects.
- Orthostatic/postural hypotension.
- Hematologic toxicities include thrombocytopenia, anemia, and neutropenia. There is no expectation for bortezomib to cause pancytopenia.
- The majority of patients experienced GI adverse events during the clinical studies, including nausea, vomiting, diarrhea, and constipation; 13% of patients experienced events that were considered serious.

NDA 21-602
Pre-Approval Safety Conference
Meeting Minutes
Page 2

Other Issues to be Addressed by ODS:

Medication error potential:

The NDA safety reviewer has concern with the 3.5mg vial size. Inadvertent administration of the entire vial to a patient of very small stature could approach the hazardous dose that caused progressive hypotension in the single-dose toxicity studies in monkeys. However, this issue is not going to delay approval of the NDA.

MEETING MINUTES – Pre-Approval Safety Conference

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Ann Farrell
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INTERNAL MEETING MINUTES

MEETING DATE: March 7, 2003 **TIME:** 10:00 AM, EST.

LOCATION: Woodmont Office Complex-2, Conference Room A

NDA# 21-602 **Request Submission Date:** February 21, 2003
Briefing Document Submission Date: February 21, 2003

DRUG: Velcade™ (bortezomib) for Injection

SPONSOR/APPLICANT: Millennium Pharmaceuticals, Inc.

TYPE of MEETING: Type-A, NDA Guidance

PARTICIPANTS:

FDA

Grant Williams, M.D.	Deputy Division Director
Ann Farrell, M.D.	Medical Team Leader
Peter Bross, M.D.	Medical Reviewer
Robert Kane, M.D.	Medical Safety Reviewer
Sean Bradley, R.Ph.	Consumer Safety Office

PURPOSE OF MEETING: To discuss Millennium's M34101-039 study protocol for Velcade.

QUESTION for DISCUSSION and DECISIONS REACHED:

1. Does the Agency agree with our proposal for non-inferiority on TTP as the primary endpoint, with the option to claim superiority if achieved?

No, superiority in TTP should remain the primary objective of study 039. To be acceptable as an endpoint for non-inferiority, the beneficial effect of the active control must have been established (see question #3). We may be able to accept similarity in survival, RR and TTP, if you can demonstrate superiority in the disease-specific clinical benefit endpoints of skeletal events and infections, but this would be a review issue.

2. Does the Agency agree with our proposal to use survival as the clinical benefit endpoint using the same methodology as for TTP?

No. Superiority in survival would be an acceptable clinical benefit endpoint. In the absence of superiority in TTP or survival confirmation of clinical benefit would be a review issue.

3. Does the Agency agree with the selected margins for the non-inferiority analysis of TTP and survival?

No. We are not convinced that the effect of dexamethasone on time to progression or survival has been adequately established in multiple myeloma, especially since the TTP endpoint in 039 has not been used in previous trials.

4. We have taken a 'conservative' approach regarding survival of patients who received dexamethasone and then are crossed-over to Velcade. Patients can receive dexamethasone for varying lengths of time including very short time frames before being switched to Velcade. We are not censoring them for the survival analysis after they are switched to Velcade. Does the Agency agree with this approach?

We agree that the primary survival analysis should be on the ITT principle, and patients who cross over should not be censored.

The following are statistical comments from the Agency regarding non-inferiority design:

1. Both TTP and survival endpoint (time to event) should be analyzed based on hazard ratio.

2. The control effect in this case can not be assessed. The assumption that median TTP in "placebo arm" = 0 is highly questionable.
3. The calculation of margin is questionable. In the fixed margin non-inferiority hypotheses, the margin should be calculated based on the control effect only. If the margin selection is also dependent on the assumption of the SE of the treatment effect, the fixed margin hypotheses are not valid because the hypotheses involve a data dependent variable (SE).
4. If both TTP and survival will lead to efficacy claim, alpha adjustment is necessary.
5. We recommend using the method proposed in [1] for this non-inferiority design.

Action Items:

The Agency's responses were forwarded to Millennium via facsimile transmission on March 14, 2003. In reaction to the Agency's responses to their questions, Millennium felt that a meeting will no longer be necessary.

Minutes prepared by: _____
Sean Bradley, R.Ph., Project Manager

Concurrence Chair: _____
Peter Bross, M.D., Medical Reviewer

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/s/

Peter Bross

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Division Director's Memorandum

Date: May 13, 2003
NDA: 21-602
Sponsor: Millenium Pharmaceuticals
Proprietary Name: Velcade® (bortezomib, PS 341) for Injection

Introduction: This NDA for the new molecular entity bortezomib (Velcade®, PS-341) for treatment of patients with multiple myeloma (MM) who have received at least two prior therapies and have demonstrated disease progression on their last therapy. PS 341 is a proteasome inhibitor; however, the precise anticancer mechanism of action has not been established.

On July 24, 1998, the initial IND was submitted. On May 23, 2002, this application received Fast Track designation for multiple myeloma. Orphan status is pending. The NDA was submitted January 21, 2003. The PDUFA goal date for this priority review is July 21, 2003.

Chemistry/Manufacturing and Controls Review: See Dr. Liang's review for details.

VELCADE™ (bortezomib) for Injection is for intravenous injection (IV) use. Each single dose vial contains 3.5 mg of bortezomib (PS-341) as a sterile lyophilized powder with 35 mg mannitol, USP.

Bortezomib is a _____

_____. The drug substance is unstable at room temperature.

The drug product contains an _____ that is adequately stable at room temperature storage. When reconstituted, bortezomib in solution exists as the _____

Post Approval Agreements. The applicant is required to provide data on melting point, optical rotation, and ethyl acetate concentration and to propose final specifications for quality control.

Chemistry/Manufacturing and Controls Review: See Dr. Liang's review for details.

VELCADE™ (bortezomib) for Injection is for intravenous injection (IV) use. Each single dose vial contains 3.5 mg of bortezomib (PS-341) as a sterile lyophilized powder with 35 mg mannitol, USP.

Bortezomib is a _____

_____. The drug substance is unstable at room temperature.

The drug product which contains an _____ which is adequately stable at room temperature storage. When reconstituted,

bortezomib in solution exists as the

Post Approval Agreements. The applicant is required to provide data on melting point, optical rotation, and ethyl acetate concentration and to propose final specifications for quality control.

Nonclinical Review:

Refer to Dr. Rosario's review and Dr. Morse's team leader memo.

Nonclinical toxicities of concern include cardiac and neurological toxicity. In both species, histopathological changes in cardiac tissue included increased incidence of perivascular necrosis, myocardial degeneration, hemorrhage, and inflammation. Also, cardiovascular safety pharmacology studies conducted in cynomolgus monkeys showed administration of dosages $\geq 3.0 \text{ mg/m}^2$ PS-341 (approximately twice the recommended clinical dose) resulted in initial physiologically significant heart rate elevations, followed by a profound, progressive hypotension, bradycardia, and death 12-14 hours post-dose. Additionally, twenty-six week studies in monkeys and rats, with a similar dose and schedule as recommended for patients, demonstrated multifocal neurotoxicity including brain dilatation, and degeneration of dorsal and ventral root ganglia, peripheral nerves, and spinal cord at doses $\geq 0.9 \text{ mg/m}^2$. Monkeys appeared to be more susceptible to the neurotoxic effects of PS-341 compared to rodents. Neurotoxicity continued to be exhibited following 8-week recovery period.

Other toxicity observed in non-clinical repeat dose studies included hematopoietic (bone marrow hypocellularity), gastrointestinal (hyperplasia and necrosis), and lymphoid system debilitation (lymphocytic depletion, atrophy, and necrosis of lymph nodes, spleen and thymus). The lethal dose and maximum tolerated dose are the same in both species. Furthermore, there is no safety margin compared to the proposed clinical dose (1.3 mg/m^2).

Velcade was assigned a Pregnancy D category based on embryoletality findings in the rat and rabbit. Bortezomib was embryoletal in rats and rabbits, at doses approximating 1/2 of the clinical dose (based on body surface area). Specifically, pregnant rabbits given PS-341 during organogenesis at a dose of 0.6 mg/m^2 experienced significant post-implantation losses and decreased numbers of live fetuses at minimally maternal toxic doses. Live fetuses from these litters also showed significant decreases in fetal weight. However, PS-341 was not teratogenic in rats and rabbits at the highest dose tested (0.5 mg/m^2 and 0.6 mg/m^2 , respectively) when administered during organogenesis. PS-341 was positive for clastogenic activity.

Phase 4 non-clinical study commitments. The sponsor will conduct studies examining

Clinical Pharmacology and Biopharmaceutic Review: See Dr. Abraham's review.

The median estimated maximum concentration of bortezomib after 1.3 mg/m² intravenous is 509 ng/ml. The pharmacokinetics as a single agent at this dose twice a week have not been evaluated. Plasma protein binding of bortezomib is 83% over the therapeutic concentration. The volume of distribution is presently unknown. In the cDNA derived microsome, the drug is metabolized by cytochrome P45, 3A4, 2D6, 2C19, 2C9, and 1A2.

Phase 4 biopharmaceutical commitments: The following studies are required: A study

Clinical and Biostatistical Review

Efficacy

See the primary review by Dr. Bross and the secondary review by Dr. Farrell.

This NDA supports Velcade monotherapy for multiple myeloma relapsing after two different therapies (with disease progression during the latest therapy). There is no approved therapy for this disease setting.

Multiple myeloma (MM) is an incurable and progressive malignancy. Remissions do not occur without treatment. Review of the published literature suggests that response duration decreases with each successive drug therapy. Patients who are "refractory" to available therapy have an estimated survival of 6-9 months.

The primary efficacy study (Study 025) was a single arm, 202 patient multi-center Phase 2 study of PS-341 administered at 1.3 mg/m² twice weekly for two weeks followed by a ten-day rest. Fourteen patients were excluded from the FDA analyses. These patients had either non-secretory myeloma (hence, could not be evaluated per response criteria below) or had received minimal prior therapy.

The Blade criteria were the protocol-specified response criteria. The Division evaluated the results according to Blade criteria (CR and PR) and the Southwest Oncology Group (SWOG) criteria (Clinical Remission). The Blade criteria were developed to evaluate response to marrow transplantation trials. The SWOG criteria have been commonly used to evaluate drug therapies (single-agent and combination regimens) Response rates according to both criteria are listed in the table below.

Efficacy Analyses for study 025

Response Analyses (VELCADE monotherapy) N=188	-N (%) -
Overall Response Rate (Blade)	52 (27.7%)
Complete Response(CR) ¹	5 (2.7%)
Partial Response(PR) ²	47 (25%)
Clinical Remission (SWOG) ³	33 (17.6%)

¹ Complete response required 100% disappearance of the original monoclonal protein from blood and urine on at least 2 determinations at least 6 weeks apart by immunofixation, and <5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks, stable bone disease and calcium.

² Partial Response requires $\geq 50\%$ reduction in serum myeloma protein and $\geq 90\%$ reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

³ Clinical Remission (SWOG) required $\geq 75\%$ reduction in serum myeloma protein and $\geq 90\%$ reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

Median time to response was 38 days or approximately 2 cycles. The median response duration CR + PR patients was substantial (365 days).

In this heavily pre-treated population (median number of prior therapies was six and 64% had received prior stem cell transplant/high-dose therapies), these results are impressive and better than expected with "available therapy." Blade Complete Responses, even at a very low rate, are unexpected with conventional chemotherapy in this patient population. The median response duration of **one year** is also impressive and clearly represents improvement over any therapies in this setting.

The Division did not take this application to ODAC because of prior ODAC discussions and approval recommendations (in other indications) based on response rates in single-arm trials that indicate clear improvements over existing therapy. The Division did consult with four hematological malignancy experts (representing academic/private practices, transplant/nontransplant practices). All consultants concurred that the above results are clearly an improvement "over available therapy." In addition, these physicians believed that the toxicity and overall risk/benefit of the drug was acceptable. Phase 4 commitments were discussed and the consultants believed that subpart H trials could potentially demonstrate clinical benefit and be performed in a timely manner after the approval and commercialization of the drug. These consultants concur with the Division's recommendation to grant accelerated approval to PS-341 under Subpart H.

Safety

The major safety findings from the two studies were asthenia, gastrointestinal complaints (diarrhea, constipation, nausea, vomiting, anorexia, and abdominal pain), hypotension, thrombocytopenia, and neuropathy. The incidences of neuropathy, diarrhea and vomiting appeared to be dose related. The incidence of neuropathy also increased with therapy duration. Clinical studies did not demonstrate significant cardiac toxicity as predicted by non-clinical studies. Dose reductions were common. Only 28% percent received a dose

of 1.3 mg/m² throughout the study. Study protocols utilized a dose modification scheme based on toxicity. This modification scheme is incorporated into instructions in labeling.

Clinical phase 4 commitments.

The following are Subpart H commitments:

- 1) Provide complete study reports on the following ongoing studies:
 - a) Study 039: "An International, Multi-center, Randomized, Open-label Study of PS-341 Versus High Dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma"
 - b) Study 029: "A Phase II Open- Label, Extension Study to Provide PS- 341 to Patients Who Previously Participated in a PS- 341 Clinical Study and Who may Benefit from Re- Treatment with or Continuation of PS- 341"
- 2) Initiate and complete a study in previously untreated multiple myeloma patients comparing Velcade alone, high-dose dexamethasone alone and combination of Velcade plus high-dose dexamethasone.
- 3) Provide follow up information to characterize the frequency, severity, and reversibility of the peripheral neuropathy on study 025, 029, and the current Velcade myeloma protocol study 039.

Additional Requests

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

Labeling issues:

The Division has suggested alternative wording for the labeled treatment indication to better match the population that was studied:

Velcade™ (bortezomib) for Injection is indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on last therapy.

Data Integrity Issues:

The Division of Scientific Investigation investigated two sites (St. Vincent Cancer Center in NY and the University of Arkansas) and found the data adequate for safety and efficacy evaluation. (See the April 17, 2003 Clinical Inspection Summary by Dr. U.)

Tradename consultation:

The tradename is acceptable to DMETS (see DMETS review).

Pediatric Considerations: Multiple myeloma does not occur in children.

Conclusions

The Division recommends accelerated approval of this NDA under Subpart H. The Velcade response rate and response duration documented in Study 025 are an improvement over results from available therapy in the indicated population and are reasonably likely to predict clinical benefit. Velcade appears to have predictable and manageable adverse events. Phase 4 studies to demonstrate the clinical benefit of Velcade are ongoing and will be able to be completed with the commercial availability of Velcade.

Richard Pazdur, MD

Director, Division of Oncology Drug Products

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Richard Pazdur
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MEDICAL OFFICER

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Division of Oncology Drug Products

Medical Team Leader's Review

NDA: 21602
Sponsor: Millennium Pharmaceuticals
Drug Product: PS 341, bortezomib, VELCADE
Projected Action Date: May 12, 2003

Background:

On January 21, 2003, Millennium Pharmaceuticals submitted this New Drug Application (NDA) for PS-341, a new molecular entity, for the treatment of relapsed and "refractory" multiple myeloma patients for accelerated approval according to 21 Code of Federal Regulations 314.500 (subpart H).

At the present time, multiple myeloma (MM) is an incurable and progressive malignancy. Each year approximately 50,000 people are alive with multiple myeloma and 15,000 people are diagnosed with multiple myeloma. Multiple myeloma is a heterogeneous disease. The disease course varies as a result of both disease- and host- related factors (e. g., age, renal function, stage, β 2-microglobulin, and chromosomal abnormalities). Remissions do not occur without treatment. MM patients may receive multiple treatments (including stem cell transplantation) over the course of their disease. The sequence of therapy and regimens used can be quite variable. Despite responses to first line or second line therapy, all patients will relapse and eventually become "refractory" to therapy. Published literature suggests that duration of response decreases with successive therapy^{1,2}. Currently, there are no effective treatments for relapsed MM patients who are considered refractory to therapy. Patients who are truly "refractory" to available therapy usually have a survival measured in months. Blade and Esteve estimated that median survival of patients with truly "refractory" disease is 6-9 months³. Because of the progressive nature of the disease, patients suffer considerable disease-related complications and morbidity from skeletal destruction as a result of lytic disease (e.g., bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, infection, neurological complications and hyperviscosity. Patients usually die as a result of their disease or infection. From the time of initial diagnosis, survival without treatment is between 6 to 12 months and extends to 3 years with chemotherapy. Patients who receive a stem cell transplant may survive even longer. However, not all patients are eligible to receive a stem cell transplant. Approximately 25% of all MM patients survive 5 years or longer, with fewer than 5% surviving longer than 10 years.

Regulatory History

On July 24, 1998, Millennium Pharmaceuticals submitted IND. for PS-341. Millennium conducted three phase 1 studies to evaluate activity and determine a dose and dose regimen.

On March 19, 2001, Millennium had an End-of-Phase (EoP) 1 meeting and discussed the development of PS-341 for the treatment of multiple myeloma and chronic leukemia.

The phase 2 studies for multiple myeloma were initiated in February 2001 and completed in June 2002.

On December 7 2001, Millennium had an EoP 1/2 meeting to discuss the preliminary data obtained, the design of a randomized trial (M34101- 039) and the approvability of PS- 341 under subpart H.

On May 23, 2002, the Agency granted Fast Track designation to PS-341.

On September 4 2002, Millennium had a second EoP 2 meeting to discuss accelerated approval of PS- 341 to treat relapsed and refractory multiple myeloma.

On December 2, 2002, Millennium presented their final phase 2 data and discussed possible submission of the phase 2 data for accelerated approval, and plans for a confirmatory trial to define clinical benefit.

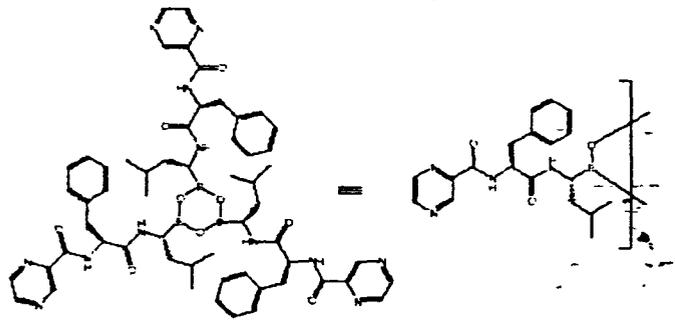
On January 21, 2003, Millennium Pharmaceuticals filed the NDA for PS-341.

Chemistry:

VELCADE (bortezomib) for Injection is a cytotoxic agent, which is available for intravenous injection as a sterile lyophilized powder in single-dose vials containing 3.5 mg bortezomib and 35 mg mannitol, USP.

Drug Substance

PS-341 is a modified dipeptidyl boronic acid derived from leucine and phenylalanine. The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.



The drug substance is manufactured by _____
 The two starting materials which establish critical _____
 in the drug substance are available commercially. The drug

Drug Product

The drug product is provided as a mannitol boronic ester, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The lyophilized drug product contains mannitol in a 10-fold excess by weight. The drug product in this form is much more stable than the drug substance itself and can be stored at controlled room temperature.

For further details, please see Dr. Liang's Chemistry, Manufacturing, and Control review of this NDA.

The following CMC phase 4 commitment issues have been identified.

1.

A

2. We acknowledge your commitment to quality control over compounds 1 and 2. We remind you to follow any appropriate regulatory submission requirements prior to changing the acceptance criteria for these starting materials.

3.

J

4.

5. Although within ICH limits, the range on ethyl acetate concentration varies ten-fold from lot to lot for the finished API (comment 16, 4/16/03). Ordinarily this would not be of major concern in the absence of related problematic data. However, other data such as:

- ◆
- ◆
- ◆
- ◆

This is in regards to your April 24, 2003 amendment regarding the identical _____ appearing in your NDA for both drug substance and drug product (V2, p.144 and V4, p.181). _____ from different samples may appear to be similar in many important aspects, but they should not be identical. It is clear from an examination of the cited _____ that they are identical down to the level of noise peaks. In that noise peaks are random, this is a highly improbable event; even more so from samples with different histories (i.e., single substance versus drug product formulation) which are evaluated at different times. **Therefore, this discrepancy remains to be resolved.**

Microbiology:

The microbiology reviewer stated "drug product is manufactured using a validated aseptic process by a manufacturer of _____ Therefore, the drug product presents a minimal risk from the standpoint of product quality microbiology".

The Microbiology review team stated this drug product could be approved from their perspective and did not identify any phase 4 commitments.

Preclinical Pharmacology and Toxicology Information:

Mechanism of Action

PS-341 is a dipeptide, boronic acid, proteasome inhibitor. PS-341 is a cytotoxic agent that reversibly inhibits the proteolytic activity of the proteasome. Thus, inhibiting the degradation of poly-ubiquitinated proteins. Inhibition prevents proteolysis, which can affect multiple signaling cascades within the cell. The disruption of normal homeostatic mechanisms can lead to cell death. The exact mechanism of action is not known.

In vitro experiments have demonstrated that bortezomib is cytotoxic to cancer cells. Bortezomib causes a delay in tumor growth *in vivo* in preclinical tumor models, including multiple myeloma.

During preclinical testing adverse events were identified. The most concerning adverse events were neuropathy and cardiac toxicity. In the repeat dose Cynomolgus monkey toxicity studies, the principal target organ effects were: severe anemia and thrombocytopenia; GI intolerance characterized by emesis and diarrhea; decreased circulating lymphocyte counts; lymphoid tissue atrophy;

- 1) Characterization of the pharmacokinetics of bortezomib as a monotherapy at the proposed 1.3 mg/m² twice-weekly dose in patients with multiple myeloma
- 2) Pharmacokinetics of bortezomib in hepatically impaired or renally-impaired patients
- 3) Evaluation of the potential drug-drug interactions (DDI) between bortezomib and commonly co-administered medications in multiple myeloma patients.

The median estimated maximum concentration of bortezomib after 1.3 mg/m² intravenous dose is 509 ng/mL. The pharmacokinetics of bortezomib as a single agent given at 1.3 mg/m² twice weekly dose has not been evaluated. Plasma protein binding of bortezomib is 83% over the therapeutic concentration. The volume of distribution is unknown. In cDNA derived microsome, the drug is metabolized by cytochrome P450 3A4, 2D6, 2C19, 2C9 and 1A2. The influence of age, gender, race and organ dysfunction on the pharmacokinetics of bortezomib has not been evaluated. Potential interactions with drugs, which are substrates, inhibitors, or inducers of the cytochrome enzymes, have not been evaluated.

A phase I dose escalation study (M34100-027) was conducted to evaluate VELCADE in combination with gemcitabine in solid tumors. In this study, VELCADE was to be given twice weekly for four weeks of each six-week cycle. Gemcitabine was administered one hour after VELCADE on day 1 and day 8 of each three-week cycle. The study demonstrated increased plasma levels of bortezomib on day 8 compared with day 1. Unfortunately it is not known whether administration of PS-341 alone results in increased plasma levels. The issue of whether accumulation occurs with repeat VELCADE exposure is unresolved and will need to be addressed by the sponsor.

Office of Clinical Pharmacology and Biopharmaceutics Phase 4 Commitments

The following phase 4 commitments are from their review:

1. Conduct a study to characterize the Pharmacokinetics (PK) of bortezomib as a single agent at 1.3 and 1.0 mg/m² twice-weekly dose in at least 12 multiple myeloma patients at each dose level. Patients should have normal to mild creatinine clearance values (50 ml/min). The pharmacokinetics should be characterized both at Cycle 1 and at a subsequent cycles to address the time dependent changes in the PK of bortezomib as a single agent.
2. Conduct a pharmacokinetic and pharmacokinetic/safety (PK and PK/Safety) study in patients with hepatic impairment to adequately provide dosing recommendations for this special patient population in the labeling for VELCADE.

3. Conduct a study to evaluate the PK and PK/safety of bortezomib in patients with advanced malignancies and varying degrees of renal dysfunction.
4. Conduct a study to evaluate the inhibition potential of bortezomib for CYP 3A4 using human liver microsomes with optimal midazolam concentration. If bortezomib significantly inhibits CYP 3A4 in *in vitro* study, the applicant may need to conduct a clinical drug interaction study to evaluate the interaction between bortezomib and midazolam or other CYP 3A4 substrate.
5. You should evaluate the contribution of cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2 in the metabolism of bortezomib using *in vitro* systems (microsomes, hepatocytes, liver, tissues, etc.). Based on the results of the study, additional drug-drug interaction studies may be required.

Clinical Studies Summary:

The table below shows the phase 1 studies submitted for review. All studies were open-label, dose escalation studies.

Study Identifier	Objectives	Patient Population	Dose escalation range and regimen
DM98-194	Determine DLT, MTD, PK, and PD, evaluate relationship between toxicity and 20S proteasome inhibition peripheral blood lymphocytes; evaluate response to treatment	53 patients with histologically confirmed malignancy for which there is no standard therapy	Dose escalation range: 0.13 –2.0 mg/m ² IV bolus 1x per week for 4 weeks, 14-day rest period (cycle - 35 days)

98-104A	Determine DLT, MTD, PK, and PD, evaluate relationship between toxicity and 20S proteasome inhibition peripheral blood lymphocytes; determine inducibility of degradation in lymphocytes; evaluate response to treatment	43 patients with histologically confirmed malignancy for which there is no proven effective therapy	Dose escalation range: 0.13 –1.56 mg/m ² IV bolus 2x per week for 2 weeks, 10-day rest period (cycle - 21 days)
LCCC 9834/00- 31	Determine DLT, MTD, and PD	27 patients with histologically confirmed hematologic malignancy who are not candidates for conventional therapy	Dose escalation range: 0.4 –1.38 mg/m ² IV bolus 2x per week for 4 weeks, 17-day rest period (cycle -42 days)

Reviewer's Table

The table below shows the phase 2 studies submitted for review.

Reviewer Comment: Although both studies permitted use of dexamethasone for those patients with stable disease (SD) or progressive disease (PD), the Agency only reviewed patient data using VELCADE alone

Phase 2 studies submitted for review

Study Identifier	Study Design	Patient Population	Primary Objective
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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	Open-label, Multicenter, Randomized trial of PS-341 at 1.0 mg/m ² vs. 1.3 mg/m ² administered as a bolus 2x per week for 2 weeks, 10-day rest period (cycle-21 days) Maximum of 8 treatment cycles	54 Multiple myeloma patients who failed to respond to or relapsed following front-line therapy	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
M34100-025: An Open-Label Phase II Study of PS-341 Alone or in Combination with Dexamethasone in Patients with Multiple Myeloma Who Have Relapsed Following Front-Line Therapy and Are Refractory to Their Most Recent Therapy (Must have 2 prior therapies)	Open-Label, Multi-center trial of PS-341 at 1.3 mg/m ² administered as a bolus 2x per week for 2 weeks, 10-day rest period (cycle-21 days) Maximum of 8 treatment cycles	202 Multiple myeloma patients who relapsed following initial front-line therapy and were refractory to most recent therapy (Must have 2 prior therapies)	To determine the response rate (the combined CR + PR + MR) following treatment with PS-341 at 1.3 mg/m ² /dose

Reviewer's Table

The sponsor also has two other ongoing studies. Study 029 is an extension study, which provides PS-341 to patients who participated in studies 024 and 025. Study 039 is a controlled study entitled: "An International, Multicenter, Randomized, Open-label Study of PS-341 Versus High Dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma."

Uncontrolled Phase I Clinical Studies:

Three phase I (DM 98-104; LCCC9834/00-31; 98-104A) and two phase II (M34100-024 and M34100-025) studies provide the primary data for the review

of efficacy and safety for single agent VELCADE. These studies determined that the MTD for biweekly administration is 1.3 mg/m².

Uncontrolled Phase II Clinical Studies:

Study Design

The main studies (024, 025) submitted in support of this application are two single arm, phase 2 studies of PS-341 alone or in combination with dexamethasone in multiple myeloma patients who have relapsed following front-line therapy. Study M34100-024 was a prospective, phase 2, randomized, multicenter study designed to evaluate the efficacy and safety of PS-341 administered at doses of 1.0 and 1.3 mg/m² given alone, or in combination with dexamethasone subsequent to inadequate response to PS-341 monotherapy, administered to patients with multiple myeloma who had failed to respond to or had relapsed following either conventional or high-dose front-line therapy. Study 025 was a prospective, phase 2, open-label, multi-center study designed to evaluate the efficacy and safety of PS-341 at a dose of 1.3 mg/m² given alone, or in combination with dexamethasone subsequent to inadequate response to PS-341 monotherapy. The primary objective of both studies was to determine the overall response rate [the combined complete response (CR) + partial response (PR) + minimal response (MR) rates] following treatment with monotherapy PS-341. An independent review committee comprised of three expert hematologists reviewed efficacy results for both studies.

Reviewer's Comment: The sponsor used the Blade criteria to describe response to PS-341 therapy⁴. Various criteria exist to describe responses observed after therapeutic intervention for MM. No standard universally accepted criteria exists to describe response in MM. Response criteria were first developed by the Committee of the Chronic Leukemia and Myeloma Task Force (CLMTF) of the National Cancer Institute in 1968. The CLMTF criteria includes a reduction in the serum and urine paraprotein of at least 50%, 50% or greater reduction in plasmacytomas, and evidence of skeletal healing. In 1972 the Southwest Cancer Chemotherapy Study Group (Southwest Oncology Group (SWOG)) devised remission criteria. The SWOG remission criteria defined 'objective response' as a reduction of at least 75% in the calculated serum paraprotein synthetic rate (rather than paraprotein concentration) and/ or a decrease of at least 90% in urinary light-chain excretion, sustained for at least 2 months⁴. Patients who had a reduction in serum paraprotein synthetic rate of between 50% and 74% were considered to have improved. Both criteria have been used for over 30 years to describe response to various treatments for multiple myeloma. Data do not exist to determine whether a 75% reduction in paraprotein synthetic rate has better prognostic significance than a 50% reduction in serum paraprotein level. In clinical practice and published literature, paraprotein concentration is used to define response because of simplicity. With use of high dose therapy,

measurable paraprotein has disappeared in a significant proportion of patients. Thus, researchers identified a need to define response criteria that included criteria for complete remission. Neither the CLMTF nor the SWOG response criteria include a definition of complete response/ complete remission (CR), since CR was rarely observed with existing non-high dose treatments. In 1998, a consensus paper was published by the Myeloma Subcommittee of the EBMT (European Group for Blood and Marrow Transplant) Chronic Leukaemia Working Party and the Myeloma Working Committee of the IBMTR (International Bone Marrow Transplant Registry) and ABMTR (Autologous Blood and Marrow Transplant Registry) to characterize responses after bone marrow transplants (autologous or allogeneic)⁴. Although Blade and others published this consensus paper, other groups continue to publish and use their own criteria to describe response to treatment. Thus, the Blade criteria are not universally accepted.

Reviewer's Comment: Although, it could be argued that the Blade criteria are more stringent because these criteria define complete response, these criteria have been available only for four years. It is not known whether complete response (Blade) could be achieved through the use of standard MM regimens such as melphalan/prednisone, vincristine/adriamycin/dexamethasone, or high dose dexamethasone. Since the Blade criteria were developed in the setting of bone marrow transplantation, the applicability of these stringent criteria to non-high dose therapy treatment is unknown. For all of the above reasons and because there is no universal consensus regarding response criteria, it is logical to use well-established and understood criteria such as the SWOG criteria to assess response to treatment for PS-341 as well.

Results

The demographics of the patient population in both trials were reviewed and consistent with the inclusion and exclusion criteria for both studies. The demographics for patient population in study 024 revealed a pre-treated population. The median number of prior therapies was 3. The demographics for patient population in study 025 revealed a heavily pre-treated population. The median number of prior therapies for patients in 025 was 6. In both studies, almost all patients had received corticosteroids (99%) and either melphalan/prednisone (approximately 92%) or vincristine/doxorubicin/dexamethasone (VAD) (approximately 81%). Eighty-three percent of study 025 patients had received prior treatment with thalidomide. Sixty-four percent of study 025 patients had undergone high dose chemotherapy with stem cell transplant (autologous or allogeneic). Forty-four percent of study 025 patients had tried other experimental therapies. The Independent Review Committee verified that all patients in study 025 were refractory to their last therapy.

Reviewer's Comment: The original intent of the protocol was to define a patient population where patients had relapsed after a front-line therapy and were considered "refractory" to their most recent therapy. The definition of "refractory"

is difficult in multiple myeloma since some patients may respond to retreatment with the same agent at relapse^{2,6,7}. However, patients do not indefinitely respond to retreatment with the same agent and eventually become refractory to that therapy. After reviewing the primary data, this patient population truly represents a population that has exhausted all available therapy and a population that demonstrated resistance to their last therapy.

For study 024, the overall response rates (CR+PR) was 30% (1.0 mg/m²) and 38% (1.3 mg/m²). For study 025, the response rates using different criteria are listed in the table below.

Reviewer's Comment: The study 025 response rates differ from the company's assessment. The Agency differed with the company and the IRC on one patient who met almost all the criteria for complete response (Blade); however, a repeat negative immunofixation was not performed. Therefore, the Agency excluded this patient. Other patients were excluded because they had non-secretory myeloma or did not receive adequate first-line therapy or a prior trial of adequate therapy. For details, see the Medical Officers' Review of this application.

Reviewer's Comment: Blade Complete Responses, even at a very low rate, are unexpected with conventional chemotherapy because these criteria were developed to evaluate results of bone marrow transplantation. These response rates would not be achieved without effective therapy as the response rate for placebo would be 0%.

Efficacy Analyses for study 025

Response Analyses (VELCADE monotherapy) N=188	N (%)
Overall Response Rate (Blade)	52 (27.7%)
Complete Response(CR) ¹	5 (2.7%)
Partial Response(PR) ²	47 (25%)
Clinical Remission (SWOG) ³	33 (17.6%)

¹ Complete response required 100% disappearance of the original monoclonal protein from blood and urine on at least 2 determinations at least 6 weeks apart by immunofixation, and <5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks, stable bone disease and calcium.

² Partial Response requires ≥ 50% reduction in serum myeloma protein and ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

³ Clinical Remission (SWOG) required ≥75% reduction in serum myeloma protein and ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

Reviewer's Table

The response rate (CR+PR) demonstrated in this population was 28% (95%CI 21, 35) with a median response duration of 365 days.

Other study 025 results are listed in the table below.

Reviewer's Comment: Both studies demonstrated that the median time to response was 38 days or approximately 2 cycles. Thus, physicians will know relatively quickly whether VELCADE will be effective for the patient.

Study 025 Efficacy Results (Including extension study data)

Median Time to Response	38 days (Min. 30, Max. 127)
Median Duration of Response (CR+PR)	365 days
Median Survival for All Patients	16 months

Reviewer's Table

The sponsor's table below shows the duration of responses seen in study 025 and the extension study 029. For individual patient data, please see the appendix to this review.

Reviewer's Comment: The table below and individual patient data suggest an impressive duration of response for some patients.

Summary of Duration of Response on PS-341 Alone (Days) by Response Category (CR, PR or MR Patients, N = 67)						
				%		
Response Category	N	Median	95% CI	Censored	Minimum	Maximum
CR+PR	53	365	(224, NE)	70	41+	509+
CR	19	365	(280, NE)	74	43	509+
CR ^{Blade}	7	**	(NE, NE)	86	61+	463
CR ^{IF+}	12	365	(280, NE)	67	43	509+
PR	34	245	(180, NE)	68	41+	369+
CR ^{SWOG}	34	463	(280, NE)	76	42+	509+
MR	14	136	(105, NE)	71	41+	483+

**Not reached

Reviewer's Table (Revised Sponsor's Table 11-14)

Reviewer's Comment: The crux of the clinical review of these studies rests on the following clinical issue: Does clinical response constitute a surrogate endpoint that is reasonably likely to predict clinical benefit? The published literature is mixed about whether attaining a clinical response particularly for relapsed and refractory patients is associated with an improvement in survival⁵⁻¹³. Review of the published literature does not suggest that any other endpoint could serve as a surrogate endpoint likely to predict clinical benefit. However, the impressive duration of response suggests that the observed response rates may predict clinical benefit.

Additional Suggestions of Efficacy from Study 025 (Exploratory Analyses)

Some patients, particularly those who developed a CR experienced:

- 1) an improvement in their hemoglobin levels with decreased transfusion need
- 2) an improvement in non-Myeloma immunoglobulins
- 3) an improvement in renal function

One patient (006-002), who achieved a complete response, was reported to have had an improvement in bone disease with radiological films demonstrating a loss of 2 lytic lesions.

Overall Safety Assessment

The safety results from the two studies suggested that with increasing dose there was increasing incidence of certain toxicities such as neuropathy, diarrhea and vomiting. Increasing duration of exposure (number of cycles of therapy) also led to increasing prevalence of neuropathy.

Reviewer Comment: Assessment of neuropathy in these studies is confounded by the fact that 70-80% of patients had a pre-existing neuropathy at study entry.

Ninety-eight percent of study 025 patients received a starting dose of 1.3 mg/m². Twenty-eight percent of these patients received a dose of 1.3 mg/m² throughout the study. Thirty-three percent of these patients who started at a dose of 1.3 mg/m² had to have their dose reduced during the study. Sixty-three percent of patients had at least one dose held during the study. Twenty-two percent of these patients discontinued because of an adverse event. The mean number of cycles administered in study 025 was six.

When the results of the two phase II studies (228 patients) were combined for the 1.3mg/m² dose level, the most commonly reported adverse events (AEs) were: nausea (64%), fatigue (65%), diarrhea (51%), thrombocytopenia (43%), constipation (43%), pyrexia (36%), peripheral neuropathy (37%), vomiting (36%), anorexia (32%), and anemia (32%). Severe or life-threatening AEs included thrombocytopenia (30%), fatigue (11%), neutropenia (3%), diarrhea (8%), and peripheral neuropathy (11%). A comparison of adverse events between the 1.3 mg/m² dose and the 1.0 mg/m² dose shows an increased frequency of neuropathy, diarrhea and vomiting 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.

During the conduct of the trial, many patients were treated expectantly for nausea/vomiting, diarrhea, constipation, and pyrexia. Doses were held or reduced for the development or aggravation of underlying neuropathy. The sponsor has provided the dosing guidelines used for study 025 in the label.

For further details, please see the Medical Officers' review of this NDA.

Clinical Phase 4 Commitments and Additional Requests

Phase 4 Commitments Under Subpart H

- 1) Provide complete study reports on the following ongoing studies:
 - a) Study 039: "An International, Multi-center, Randomized, Open-label Study of PS-341 Versus High Dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma"
 - b) Study 029: "A Phase II Open- Label, Extension Study to Provide PS-341 to Patients Who Previously Participated in a PS- 341 Clinical Study and Who may Benefit from Re- Treatment with or Continuation of PS- 341 Therapy"
- 2) Initiate and complete a study in previously untreated multiple myeloma patients comparing VELCADE alone, high-dose dexamethasone alone and combination of VELCADE plus high-dose dexamethasone.
- 3) Provide follow up information to characterize the frequency, severity, and reversibility of the peripheral neuropathy on study 025, 029, and the current VELCADE myeloma protocol study 039.

Additional Requests

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

Oncology Drugs Advisory Consultants

We discussed this application with four Agency consultants.

The consultants were: Dr. Bruce Cheson, Dr. C. Karanes, Dr. Harvey Katzen, and Dr. Donna Przepiorka. We could not discuss the application with the patient consultant, Mr. Michael Katz, because he had omitted information about a potential conflict of interest when he was originally cleared by the Advisors and Consultants' staff.

The consultants received the following questions:

1. Entry criteria state that patients are to be "Relapsed following a response to standard first-line chemotherapy (e.g., VAD or MP) or first-line high-dose chemotherapy..." Therefore, the population in reference to prior treatment is heterogeneous. The Division has allowed accelerated approval based on response rates in single arm trials when no other available therapy exists (e.g. initial CPT-11 approval in the 5-FU refractory population). Does the patient population defined in study 025 meet this criteria?

2. Do you believe the efficacy data and safety profile as presented are reasonably likely to predict clinical benefit and thus support registration and marketing approval under subpart H?

Unanimously the four consultants agreed that the patient population in the study represented a patient population for whom no available therapy exists. Also, they unanimously agreed that the efficacy data as presented were reasonably likely to predict clinical benefit and thus support registration and marketing approval under subpart H.

All commented that patients achieving some measure of response (e.g., CR or PR) would have prolonged survival over non-responders.

Conclusions and Recommendations

Discussion

The sponsor seeks an accelerated approval for a treatment indication for a relapsed and refractory multiple myeloma patient population. As stated above, the definition of "refractory" is difficult to determine in multiple myeloma. However, the Independent Response Committee reviewed all data concerning the last therapy that patients had received and determined that these patients were refractory to their last therapy.

The Study 025 response rate (CR+PR) demonstrated in this population was 28% (95%CI 21, 35) with a median response duration of 365 days. In this patient population, the likelihood of response to an ineffective therapy is 0%.

The DODP has accepted applications for accelerated approval containing single arm trials demonstrating response in a refractory disease setting. The Agency has accepted that response rates with a reasonable duration as a surrogate endpoint "reasonably likely" to predict clinical benefit.

For accelerated approval, the treatment regimen also should be better than available therapy. In this population, there is no therapy that would be considered available therapy. The demographics for patient population in study 025 revealed a heavily pre-treated population. The median number of prior therapies for patients in 025 was 6. In both studies, almost all patients had received corticosteroids (99%) and either melphalan/prednisone (approximately 92%) or vincristine/doxorubicin/dexamethasone (VAD) (approximately 81%). Eighty-three percent of study 025 patients had received prior treatment with thalidomide. Sixty-four percent of study 025 patients had undergone high dose chemotherapy with stem cell transplant (autologous or allogeneic). Forty-four percent of study 025 patients had tried other experimental therapies. This patient population has exhausted all other options for available therapy. Clearly the studies demonstrated that VELCADE was better than available therapy.

Conclusion

Review of the efficacy and safety results from studies 024 and 025 suggest that VELCADE is an effective therapy and better than available therapy for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on prior therapy. There is no available therapy for these patients. Review of the literature suggests that response in a relapsed and "refractory" patient population may be predictive for survival. Based on a review of the VELCADE data, review of the literature, and discussions with the ODAC consultants, I recommend the approval of VELCADE under subpart H.

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Appendix
Additional Tables from the Sponsor's NDA

Table 2.7.3-22 Patient Listing of IRC Determined CR ^{Blade} and CR ^{IF+} to Treatment with PS-341 Alone (Study M34100-025)							
	Number of	Best Response		TTP on Last		TTP including	Survival ^a
Response	Prior	to Any		Prior	TTP on	extension	on PS-
Pt ID	Regimens	Prior Rx	Last Prior Therapy	Therapy	PS-341	data	341
CR ^{Blade}							
02-0015	11	CR	IMiD	62	192 ^b	309+	354+
03-0001	10	CR (BMT)	Prednisone	244	175 ^b	401+	449+
03-0021	2	PD	VAD	32	157 ^b	338+	378+
03-0033	3	PD	Prednisone	519	266+	266+	266+
06-0002	5	PR	Dexamethasone pulse	93	500	500	532+
12-0027	4	CR	Thalidomide / Dex	62	108+	108+	180+
14-0015	4	CR (BMT)	Biaxin/Adria/Decadron	32	379+	379+	379+
CR ^{IF+}							
02-0009	5	PR	Cyclophosphamide /VP1	60			
						307+	307+
02-0028 ^c	5	PR	Thalidomide	732	136 ^b	136 ^d	305+
03-0005 ^c	8	CR (BMT)	Biaxin /Dex/Thalidomide	90	78	78	202
03-0015	4	NC	Thalidomide / Pred	338	155+	155+	155+
03-0019	9	PR	Arsenic trioxide	30	125 ^b	388+	388+
03-0028 ^c	7	PR	Biaxin/Dex/Thalidomide	93	118 ^b	118 ^d	296+
06-0006	6	PR	Melphalan	30	392+	392+	392+
06-0009	6	PR	Thalidomide / Pred	612	400	400	442+
06-0010	15	CR (BMT)	Doxil / Navelbin	90	188	188	451+
06-0011	4	PR	Thalidomide	60	322	322	448+
06-0022	4	CR (BMT)	Thalidomide	731	286+	286+	286+
14-0006	8	PR	Cisplatin/VP-16	54	547+	547+	547+

Source: M34100-025, section 16.1.15, IRC Patient Profiles; section 16.2.4, Data Listing 16.2.4.5C; section 16.2,

Data Listing 16.2.6.1A and Data Listing 16.2.6.1B; section 2.7.3.6.2, Listing 2.3.7.6.
a Survival on PS-341 alone or in combination with dexamethasone.
b Patients entered Study M34101-029.
c Patients received PS-341 in combination with dexamethasone; results presented for response, duration of response and time to progression are based on treatment with PS-341 alone.
d Received dexamethasone at the start of the extension study; data were censored in the analysis.
Note: Patient numbers presented in bold font were enrolled in Cohort 2.

Response	No. of		TTP		TTP w/	
Pt ID	Regimens	Last Prior Therapy	Last Prior Therapy	TTP on PS-341	extension data	Survival ^a
001-0001	12	Farnesyltransferase inhibitor	93	261+ ^b	353+	395+
001-0002	6	Semaxanib	31	261+ ^b	297	360+
001-0005	5	Thalidomide/Dexamethasone	93	213+ ^b	322+	322+
002-0001	2	Melphalan/Prednisone	515	325+	325+	325+
002-0011	11	SU5416	31	161+ ^b	234+	302+
002-0013	9	Thalidomide	32	185+ ^b	185+ ^d	381+
002-0018	10	DT-PACE	143	179+	179+	179+
002-0021 ^c	11	SU5416	185	133+	133+	254+
002-0026 ^c	4	Melphalan	30	137	137	228+
002-0029	3	Thalidomide	124	131+ ^b	264	307+
003-0011	3	Biaxin / Prednisone	152	177+ ^b	381	427+
003-0012	6	Decadron/Thalidomide/Biaxin	152	185+ ^b	437+	437+
003-0024	3	Dapsone/Decadron	1185 ^e	171+	171+	171+
004-0006	7	Thalidomide /Decadron	213	331+	331+	331+
005-0009	5	Melphalan/Dex/Thalidomide	671	213	213	374+
006-0017	6	Alkeran / Prednisone	91	405+	405+	405+
007-0003 ^c	6	Thalidomide / Dexamethasone	32	84+	84+	192
007-0008 ^c	7	Thalidomide/Prednisone	123	147	147	212
007-0010	8	Thalidomide/Dexamethasone	123	279	279	304+
008-0006	9	VAD + BCNU	63	233	233	295

009-0003	8	Cytoxan/Dexamethasone	32	177+	177+	428+
009-0005	6	Cytoxan	32	176	176	478+
009-0011	7	IMiD	185	296+	296+	296+
009-0013	6	Cytoxan	62	281	281	309+
011-0004	8	Decadron	1070 ^e	119	119	135
012-0003 ^c	6	Thalidomide/Dexamethasone	213	77+	77+	210
012-0008	6	Thalidomide	90	123+	123+	403+
012-0012	5	Thalidomide	517	402+	402+	402+
012-0013	3	Thalidomide	518	219	219	366+
012-0020 ^c	11	CC5013 + Prednisone	184	159	159	256
012-0021 ^c	3	Thalidomide	62	119	119	237
						Continued

	No. of		TTP		TTP w/	
Response	Prior		Last	TTP	extension	
Pt ID	Regimens	Last Prior Therapy	Therapy	PS-341	data	Survival ^a
012-0025 ^c	9	Cytoxan	31	154+ ^b	154+ ^d	304+
014-0011	3	Biaxin / Prednisone	32	458+	458+	458+
014-0019	2	Biaxin / Decadron / Thalidomide	122	311+	311+	311+

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/s/

Ann Farrell
5/9/03 03:38:42 PM
MEDICAL OFFICER

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Demographic Worksheet

Application Information (Enter all identifying information for the submission pertaining to this summary)

NDA Number: 21-602

Submission Type: N/A (pilot)

Serial Number: N/A (pilot)

Populations Included In Application (Please provide information for each category listed below from the primary safety database excluding PK studies)

CATEGORY	NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG	
Gender	Males	121	All Females	81	Females >50	66
Age:	0-≤1 Mo.	0	>1 Mo.-≤2Year	0	>2-≤12	0
	12-16	0	17-64	131	≥65	71
Race:	White	164	Black	21	Asian	5
	Other	12				

Gender-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?			
	If analysis was not performed, please provide comment below.			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on gender recommended in the label?

If the analysis was completed, who performed the analysis

Was gender-based analysis included in labeling?	
YES	NO
<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>

Yes

No

Sponsor

FDA

Age-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?			
	If analysis was not performed, please provide comment below.			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on age recommended in the label?

If the analysis was completed, who performed the analysis

Was age-based analysis included in labeling?	
YES	NO
<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input checked="" type="checkbox"/>	<input type="checkbox"/>

Yes

No

Sponsor

FDA

Race-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?			
	If analysis was not performed, please provide comment below.			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on race recommended in the label?

If the analysis was completed, who performed the analysis

Was race-based analysis included in labeling?	
YES	NO
<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>

Yes

No

Sponsor

FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

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/s/

Peter Bross
5/12/03 12:42:07 PM

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PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA # 21-602 _____ Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-150 Trade and generic names/dosage form: VELCADE (bortezomib) for Injection Action: AP

Applicant Millennium Pharmaceuticals, Inc. Therapeutic Class antineoplastic agent

Indication previously approved none

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Proposed indication in this application Multiple Myeloma

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION. IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___ Yes (Continue with questions) X No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
___ Neonates (Birth-1month) ___ Infants (1month-2yrs) ___ Children (2-12yrs) ___ Adolescents(12-16yrs)

- 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ___ No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical

review, medical officer, team leader)

Signature of Preparer and Title

Date

cc: Orig NDA # 21-602
HFD-150/Div File
NDA Action Package
HFD-960/ Peds Team
(revised 1-14-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 4-7337

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/s/

Arn Farrell
5/13/03 04:13:10 PM

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 17, 2003

TO: Sean Bradley, Regulatory Health Project Manager
Ann Farrell, M.D., Medical Officer, Clinical Reviewer
Peter Bross, M.D., Medical Team Leader, Clinical Reviewer
Division of Oncology Drug Products, HFD-150

THROUGH: Tony El-Hage, Ph.D., Associate Director, Good Clinical Practice
Branch I & II (HFD-46/47), Division of Scientific Investigations

FROM: Khin Maung U, M.D., Acting Branch-Chief, Good Clinical
Practice Branch I (HFD-46), Division of Scientific Investigations

SUBJECT: Evaluation of Foreign Domestic Inspections

NDA: 21-602

APPLICANT: Millennium Pharmaceuticals, Inc.

DRUG: Velcade™ (bortezomib) for injection

CHEMICAL CLASSIFICATION: Type 1, P

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of relapsed and refractory multiple myeloma

CONSULTATION REQUEST DATE: February 10, 2003

GOAL DATE TO PROVIDE
INSPECTION SUMMARY REPORT: May 5, 2003

PDUFA GOAL DATE: July 21, 2003

I. BACKGROUND

Velcade™ (bortezomib) is a new molecular entity that belongs to a class of compounds known as proteasome inhibitors. The sponsor plans to market it with the indication of treatment of relapsed and refractory multiple myeloma. This submission was an e-NDA. One pivotal study M34100-025, an open-label, non-randomized, single-arm study, was submitted in support of this e-NDA.

II. RESULTS (by site):

NAME	CITY, STATE	COUNTRY	PROTOCOL	INSPECTN DATE	EIR RECD.	CLASSN.
Sundar Jagannath, M.D.	New York, NY	USA	M34100-025	March 6-13, 2003	Apr 4, 2003	VAI
Barry Barlogie, M.D., Ph.D.	Little Rock, AR	USA	M34100-025	April 2-4, 7-10, 15, 2003	Pending	NAI

Study Protocol - M34100-025: An Open-Label Phase II Study of PS-341 Alone or in Combination with Dexamethasone in Patients with Multiple Myeloma Who Have Relapsed Following Front-Line Therapy and Are Refractory to Their Most Recent Therapy.

This is an open-label, non-randomized, single-arm study. The study was conducted at 14 centers in the U.S.

The primary efficacy outcome was the overall response rate [the combined complete response (CR) + partial response (PR) + minimal response (MR) rates] following treatment with monotherapy PS-341 at 1.3 mg/m²/dose in patients with multiple myeloma who had relapsed following initial front-line therapy and were refractory to their most recent therapy.

A treatment cycle consisted of four injections of PS-341 (given twice per week, e.g., on Monday and Thursday, on Days 1, 4, 8 and 11) followed by a 10-day rest period (total of 3 weeks or up to 8 cycles (of 3 weeks each) of treatment could be administered. After the first two treatment cycles, dexamethasone could be added to the patient's treatment regimen for patients with a suboptimal response to PS-341 alone. Patients who were, in the investigators' opinion, benefiting from PS-341 treatment in the current study were eligible to continue PS-341 treatment in an extension study (M34101-029).

The sponsor reported an overall response rate (CR+PR+MR) to treatment with PS-341 alone of 33% in cohort 1 (25 of 76 patients), and this response rate was confirmed in cohort 2 with an overall response rate of 36% (42 of 117 patients).

Basis for site selection: The following sites were selected for inspection because of their high enrollment and relatively large response rates.

(1) **Sundar Jagannath M.D.**

St Vincent's Comprehensive Cancer Center (number enrolled: 22 subjects)
325 West 15th Street, New York, NY 10011

Inspection Dates: March 6-13, 2003

Methodology: Inspection assignments were issued to the field office.

a. What was inspected

24 four subjects were screened for the study; 22 were enrolled. The field investigator examined complete study records for 8 of the 22 subjects enrolled, and compared case report forms to source documents for the 8 subjects.

b. Limitations of inspection: None.

c. General observations/commentary

CRFs accurately reflected data recorded in source documents. All 8 subjects' records that were inspected were found to have the condition required for the study and met inclusion/exclusion criteria.

Concomitant medications and AEs were reported accurately.

All 22 records were reviewed for existence of informed consent. All consents were signed prior to study entry and consent updates were signed appropriately.

The inspection revealed that three subjects were under-dosed for 2 to 4 cycles of treatment. The protocol called for subjects to receive PS-341 at a dosage of 1.3mg/m² based on Body Surface Area (BSA) which was calculated on the subject's height and weight at each treatment visit. The following table shows the amount of drug given, the amounts that should have been given based on the protocol formula, and the percentage of under-dosage:

Subject	Cycle	Dose (mg) given	Dose (mg) per protocol	% underdose
006	I	2.14	2.29	7
	II	2.17	2.35	8
	III	2.17	2.36	8
	IV	2.17	2.38	9
009	I	2.00	2.30	13
	II	2.00	2.30	13
	III	2.00	2.30	13
	IV	2.00	2.26	11
011	I	2.40	2.54	6
	II	2.40	2.54	6

Dr. Jagannath responded to the 483 item in a letter dated March 24, 2003 in which he explained the discrepancies in the data for the above subjects as follows:

006 - The dose was calculated on ideal rather than actual body weight.

009 - The subject's height that was 5'7" recorded as 57" not 67". The error was discovered by the pharmacy, and the sponsor and the IRB were notified. Dr. Jagannath stated that the subject was responding to the drug treatment and continued in the study. The correct dosage was given in Cycle V.

011 - There was an error in the BSA calculation. The BSA was 1.98 m² and was mistakenly rounded to 1.9 m².

No other significant deviations were noted.

Recommendation: Data from this site are acceptable.

(2) **Barty Barlogie, M.D., Ph.D.**

University of Arkansas for Medical Sciences
Arkansas Cancer Research Center
4301 West Markham, Slot 776, Little Rock, Arkansas 72205

Inspection Dates: April 2-4, 7-10, 15, 2003

Methodology: Inspection assignments were issued to the field office.

a. What was inspected

Thirty-three subjects were enrolled. The case report forms were examined and compared to source documents to verify disease states.

b. Limitations of inspection: None.

c. General observations/commentary

No FDA-483 was issued. (EIR not yet available. Information was obtained from FDA field investigator by e-mail.)

While there were a few issues with study records (transcription problems), they were identified and addressed and did not affect the study data. No significant deviations were noted. A review of the informed consent document revealed it contained all the required elements of informed consent.

Recommendation: Data from this site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

I conclude that there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, and were available for the duration of the study, and that all enrolled subjects received the assigned study medication, had clinical and laboratory parameters recorded, completed the study, and had their primary efficacy endpoints captured as specified in the protocol and correctly reported to the sponsor.

I recommend that data from the two sites that were inspected can be used for the evaluation of Study Protocol M34100-025 submitted in support of NDA 21-602 for review by FDA.

[Note: This Clinical Inspection Summary was based on the inspectional findings (FDA Form 483) and discussions with the investigator at the site in Little Rock, Arkansas and one EIR received following inspection of Dr. Jaggannath's site. Should the EIRs and exhibits from the sites, when received, contain additional information that would significantly effect the classification or have an impact on the approval process, I will inform the Review Division in an amendment.]

Khin Maung U, M.D.
Branch Chief, Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:
Supervisory comments

Antoine El-Hage, Ph.D.
Associate Director, Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations

DISTRIBUTION:
NDA 21-602
HFD-45/Division File
HFD-45/Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-47/El-Hage/U/ Currier
HFD-47/Balser GCPB2 Files #10861, and # _____

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/s/

Sherry George

4/17/03 02:57:56 PM

TECHNICAL

Signed by Dr's El-Hage and U on 4/17/03

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 4, 2003

FROM: Richard Pazdur, M.D. /S/
Director
Division of Oncology Drug Products, HFD-150

TO: Director, Division of Scientific
Investigations, HFD-340

SUBJECT: Request for Clinical Inspections for NDA 21-602
Velcade™ (bortezomib) for Injection
Indication: VELCADE™ (bortezomib) for Injection is indicated for the
treatment of relapsed and refractory multiple myeloma.

We have identified the attached studies as being pivotal to the approval of this application.
Attached is the list of studies and sites.

We request that the inspections be performed and the Inspection Summary Results be provided
by April 1, 2003. We intend to make a regulatory decision on this application by April 18, 2003.

Should you require further information please contact:

Tanya Lewis, M.Sc.
Senior Manager, Regulatory Affairs
Worldwid Regulatory Affairs & Pharmacovigilance
Phone: 617-551-8951
Fax: 617-551-3742

The reviewing medical officer for this application is Peter Bross, M.D., (301-594-5768).

The responsible project manager/CSO is Sean Bradley (301-594-5770).

The user fee goal date is July 21, 2003. Dr. Pazdur requests an expeditious inspection because he
would like to take an action on this application as early as April 2003.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION
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TO (Division/Office) Microbiology, Dr. P. Cooney (HFD-160)	FROM: Chengyi Liang, Oncology Drug Products HFD-150
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DATE 1/15/03	IND NO.	NDA NO. 21-602	TYPE OF DOCUMENT original	DATE OF DOCUMENT 1-10-03
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NAME OF DRUG alcade for Injection	PRIORITY CONSIDERATION bortezomib	CLASSIFICATION OF DRUG Anticancer agent	DESIRED COMPLETION DATE 4-30-03
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NAME OF FIRM: Millennium Pharmaceuticals, Inc

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> OTHER (Specify below) |
|--|--|--|

II. BIOMETRICS

- | | |
|--|--|
| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER | <input type="checkbox"/> CHEMISTRY
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER |

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO MAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

- | | |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE eg POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary): Please review the microbiological test data and test method for DP cc:
 Orig NDA 21-602
 HFD-150/Div. File
 HFD-150/RLostritto
 HFD-150/CLiang
 HFD-150/SBradley

SIGNATURE OF REQUESTER SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND SIGNATURE OF DELIVERER
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