

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602

CORRESPONDENCE



Sundar Jagannath, M.D.
St. Vincent's Hospital
Comprehensive Cancer Center
325 West 15th Street
New York, New York 10011

APR 18

Dear Dr. Jagannath:

Between March 6 and 13, 2003, Mr. Thomas P. Hansen, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # M34100-025, entitled: "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") of the investigational drug Velcade (bortezomib), performed for Millennium Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Hansen presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge your letter dated March 24, 2003, in response to the Form FDA 483. We wish to emphasize the following:

1. You did not follow the protocol [21 CFR 312.60]. Drug dosages for subjects 006, 009, and 011 were not calculated according to the instructions in the protocol. We accept your response and the explanation for the errors made in the dose calculation.
2. You did not ensure that the consent form used in the study contained all required elements of informed consent [21 CFR 50.25(a)(5)]. The consent form must contain a statement that FDA may inspect subject records. To simply state that "authorized representatives from regulatory agencies...will have access to...medical records for the purpose of verifying data collected for the study" is not sufficient. FDA must be specifically identified by name.

In addition, we wish to comment on your statement during the inspection that records for the M34100-025 study would be kept for 10 years. For your information, federal regulations require that study records be kept for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified [21 CFR 312.62(c)]. Please make sure you retain study records for the required length of time or consult with your sponsor on the status of record retention.

Page 2 - Sundar Jagannath, M.D.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Hansen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice Branch I, by letter at the address given below.

Sincerely,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 3 - Sundar Jagannath, M.D.

FEI: 3003973917

Field Classification: VAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

Deficiencies noted:

- inadequate informed consent form (03)
- failure to adhere to protocol (05)
- other (18; please specify: Inadequate procedures for records retention. The investigator had actually not violated the regulation yet.) :

cc:

HFA-224
HFD-150 Doc.Rm. NDA# 21-602
HFD-150 Review Div.Dir. (Pazdur)
HFD-150 MO (Bross)
HFD-150 PM (Bradley, Sean)
HFD-46/47c/r/s/ GCP File # 10861
HFD-46/47 GCP Reviewer (U)
HFD-46/47 CSO (Currier)
HFR-NE100 DIB (Woysner)
HFR-NE1500 Bimo Monitor/Investigator (Hansen)
GCF-1 Seth Ray

r/d:CAC:4/7/03

reviewed:KMU:4/8/03

reviewed:AEH:4/10/03

f/t:sg:4/7/03;4/9/03; ML:4/10/03;sg:4/14/03

o:\cac\jagannathLTR.doc

Reviewer Note to Rev. Div. M.O.

This inspection was one of two assigned to verify data for NDA 21-602. In general, the study was found to be well run and adequately documented. Problems found during the inspection consisted of the improper wording of the informed consent and incorrect records retention procedures.

There was one problem with drug dosage. The protocol specified the amount of drug to be administered as $1.3\text{mg}/\text{m}^2$. For 3 of 22 subjects, the BSA or dosage was incorrectly calculated so that the subjects were under-dosed. See below for details.

<u>SUBJECT</u>	<u>CYCLE</u>	<u>AMT. GIVEN (MG)</u>	<u>AMT. REQUIRED BY PROTOCOL (MG)</u>	<u>% UNDER DOSAGE</u>
006	I	2.13	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

- The miscalculation of BSA, which resulted in the under-dosing, was corrected by Cycle V.

It appears the under-dosage is small, and since it occurred in only 3 subjects, it would appear that the significance on the study results would be negligible. This being the case, it appears that the data from the study could be used to support an approval decision for the pending NDA.

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Antoine El-Hage
4/18/03 11:37:32 AM

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

113-003

MILLENNIUM PHARMACEUTICALS, INC.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.millennium.com

RECEIVED

February 07, 2003

FEB 11 2003



MILLENNIUM

Khin Mating U, M.D.
Medical Officer
Division of Scientific Investigations (HFD-45)
7520 Standish Place, Room 125
Rockville, MD 20855

HFD-150 / CDER

RECEIVED

FEB 10 2003

CDR/CDER

RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Information Amendment
Serial Number: 002

Dear Dr. U:

In response to a fax received on Friday, January 31, 2003 from Mr. Sean Bradley enclosed please find information relating to the pivotal study for eNDA # 21-602. This eNDA was submitted for VELCADE™ (bortezomib) for Injection on January 21, 2003. The day 45 meeting is scheduled for March 5, 2003 and the action date is July 21, 2003. We have requested and expect priority review of the eNDA. VELCADE is a new molecular entity that belongs to a class of compounds known as proteasome inhibitors indicated for the treatment of relapsed and refractory multiple myeloma.

In support of the VELCADE eNDA, one pivotal study M34100-025 was submitted and will be the subject of this information amendment. This study was an open-label, non-randomized study, single arm study. Therefore, the request for randomizations lists and total number of study subjects in each study arm is not applicable to this application.

Please note that the eNDA was submitted in the CTD format there is not a Volume 1.1. As agreed to during our conversation on February 5, 2003, I have included the clinical summary of the CTD which discusses the clinical data in detail that was provided in the eNDA. In addition, we have provided a one paper copy for the office, one paper copy for the field and one CD-ROM will be submitted to the electronic document room.

If you have any questions regarding this submission or require additional information or copies, please feel free to contact me at 617-551-8951.

Sincerely,

Tanya Lewis, M.S.
Senior Manager, Regulatory Affairs
Millennium Pharmaceuticals, Inc.



DEPARTMENT OF HEALTH & HUMAN SERVICES

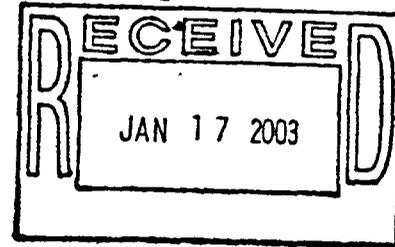
Public Health Service

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

January 15, 2003

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139

Attention: Tanya Lewis, MS
Senior Manager, Regulatory Affairs



Re. Designation Request # 02-1630

Dear Ms. Lewis:

Reference is made to your request for orphan-drug designation dated September 30, 2002, of bortezomib for the treatment of multiple myeloma. Please also refer to our acknowledgement letter dated November 18, 2002.

We have completed the review of the information submitted in your original request and we have determined that bortezomib qualifies for orphan-drug designation for the treatment of multiple myeloma. Please note that it is bortezomib and not its formulation that has received orphan-drug designation. You have notified us that you are currently developing bortezomib under the trade name Velcade™.

Please be advised that if bortezomib is approved for an indication broader than the orphan-drug designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of bortezomib as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved (21 CFR 316.30). If you need further assistance in the development of your product for marketing, please feel free to contact Donald R. Haggerty, MD, MPH, at (301) 827-3666.

Please refer to this letter as official notification and congratulations on obtaining your orphan-drug designation.

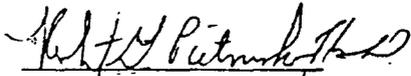
Sincerely yours,

/S/

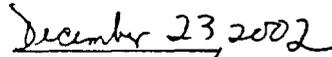
Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

Debarment Certification

Millennium Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Robert Pietrusko, PharmD
VP, Worldwide Regulatory Affairs &
Pharmacovigilance



Date

Patent Certification

In accordance with 21 CFR 314.53(c)(2) , the following declaration is provided:

The undersigned declares that Patent Numbers US 5,780,454; 6,083,903; and 6,297,217 cover the formulation, composition, and/or method of use of VELCADE™ (bortezomib) for Injection. This product is the subject of this application for which approval is being sought.



Scott A. Brown
Vice President, Chief Patent Counsel
Millennium Pharmaceuticals, Inc.

Patent Information

Patent information as specified in 21 CFR 314.53(c)(1) is summarized as follows:

US Patent Number	Expiration Date	Type of Patent	Patent Owner
5,780,454	October 28, 2014	Drug Product	Millennium Pharmaceuticals, Inc.
6,083,903	October 28, 2014	Drug Product, Method of Use	Millennium Pharmaceuticals, Inc.
6,297,217	October 28, 2014	Method of Use	Millennium Pharmaceuticals, Inc.

Claimed Exclusivity

Pursuant to 21 CFR 314.108(b)(2) Millennium Pharmaceuticals Inc. is hereby claiming exclusivity for VELCADE™ (bortezomib) for Injection.

Millennium Pharmaceuticals Inc. hereby certifies that to the best of its knowledge no drug has been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act that contains bortezomib, the active moiety in VELCADE:


Robert Pietrusko, PharmD
VP, Worldwide Regulatory Affairs &
Pharmacovigilance

Dec. 31, 2002
Date

Millennium Pharmaceuticals, Inc
 75 Sidney Street
 Cambridge, MA 02139
 Tel 617 679-7000
 mlnm.com

Facsimile Transmittal



TO	Sean Bradley	FAX	(301) 594-0498 9
FROM	Tanya Lewis	DATE	28 January 2003.
RE	Press Release - Submission New Drug Application for VELCADE™ (Bortezomib) for Injection		
CC		PAGES	4 including cover sheet
Urgent	<input checked="" type="checkbox"/> For Review	<input type="checkbox"/> Please Comment	<input type="checkbox"/> Please Reply <input type="checkbox"/> FYI

MESSAGE:

Mr. Bradley:

Attached is the press release for our New Drug Application for VELCADE™ (Bortezomib) for Injection submission.

If you have any questions, please contact me at 617-551-8951.

Tanya Lewis, M.S.
 Senior Manager
 World Wide Regulatory Affairs and Pharmacovigilance
 Millennium Pharmaceuticals, Inc.

Confidential: This transmittal is intended only for the use of the addressee(s) named above. If the reader of this transmittal is not the intended recipient, or the employee or agent responsible for delivering the transmittal to the intended recipient(s), please note that any distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone, and return the original to us by mail at the above address.



Millennium Pharmaceutical, Inc.
 75 Sidney Street
 Cambridge, Massachusetts 02139
 617 679.7000
 www.millennium.com

NEWS RELEASE

FOR RELEASE WEDNESDAY, JANUARY 22, 2003 AT 7:59 AM

Contacts:

Steve Sylven (media)
 (617) 551-8984

Gina Price Nugent (investor)
 (617) 551-3611

**MILLENNIUM SUBMITS NEW DRUG APPLICATION FOR VELCADE™
 (BORTEZOMIB) FOR INJECTION**

-- Novel therapy also granted Orphan Product Designation --

Cambridge, Mass., January 22, 2003 -- Millennium Pharmaceuticals, Inc. (Nasdaq: MLNM) today announced that it has submitted a New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) for approval to market VELCADE as a treatment for relapsed and refractory multiple myeloma. In June 2002, VELCADE was granted fast-track status by the FDA as having the potential to treat a serious, life-threatening condition and address an unmet medical need. The NDA was submitted under the provisions of Subpart H - Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses.

The NDA filing for VELCADE is based primarily on the results of the Company's phase II SUMMIT clinical trial, a multi-center study which included 202 patients with relapsed and refractory multiple myeloma. The results of this trial were presented in full at the December 2002 meeting of the American Society for Hematology.

What's Next for VELCADE?

While the NDA filing marks the end of one process, it also represents the advent of another. [Read more.](#)

What is VELCADE?

And how does it work? [Read more.](#)

"The submission of this NDA represents a significant milestone for Millennium and an important step toward fulfilling our mission of making novel treatment options available to patients with significant unmet medical needs," said Robert Tepper, M.D., president, research and development at Millennium. "Since the initial VELCADE patient dosing

Millennium submits New Drug Application for VELCADE™ (bortezomib) for Injection

just over four years ago, we have been committed to the thorough and expeditious clinical development of VELCADE and are proud that this strategy has resulted in an accelerated filing.”

Orphan Product Designation

VELCADE™ (bortezomib) for Injection has also received Orphan Product Designation from the FDA for multiple myeloma. Orphan Product Designation is granted for treatments that may provide significant benefit to patients with serious life-threatening diseases that have a prevalence of no more than 200,000 patients in the U.S. Upon FDA approval of the product, Orphan Product Designation provides seven-year marketing exclusivity in the U.S.

Recent VELCADE News

Millennium recently initiated two phase II trials with VELCADE: one in patients with metastatic colorectal cancer and another in patients with advanced non-small cell lung cancer. In addition, the Company has an ongoing international, multi-center, phase III (APEX) trial of VELCADE in patients with multiple myeloma as well as several phase I/II trials in patients with various hematologic and solid tumors. The Company also plans to initiate additional phase I/II studies later this year.

VELCADE is designed to specifically block the proteasome, which is an enzyme complex in cells responsible for breaking down a variety of proteins, including many that regulate cell division. In pre-clinical studies, inhibition of the proteasome has been shown to lead to the disruption of cell cycle progression, resulting in cancer cell death (apoptosis). VELCADE is the first and only proteasome inhibitor currently being evaluated in clinical trials for the treatment of cancer.

For more information about VELCADE clinical trials, patients and physicians can contact the Millennium Medical Product Information Department at (800) 589-9005.

About Multiple Myeloma

Multiple myeloma is a cancer of the bone marrow in which white blood cells called plasma cells, normally responsible for the production of antibodies (proteins that fight infection and disease), are overproduced. The proliferation of these abnormal plasma cells, known as myeloma cells, causes decreased production of normal red and white blood cells, and of normal disease-fighting antibodies, as well as the growth of tumors that spread to multiple sites – hence the term multiple myeloma. The decreased white blood cell production damages the immune system while the myeloma tumors cause bone destruction that manifests as pain and fractures.

Multiple myeloma is the second most common hematologic malignancy and although the disease is predominantly a cancer of the elderly (the average age of onset is 65 to 70 years of age), recent statistics indicate both increasing incidence and younger age of onset. In the United States, more than 40,000 individuals have multiple myeloma and over 14,000 new cases of the disease are diagnosed each year. Worldwide there are

Millennium submits New Drug Application for VELCADE™ (bortezomib) for Injection

approximately 74,000 new cases and more than 45,000 deaths due to multiple myeloma each year.

About Millennium

Millennium Pharmaceuticals Inc., a leading biopharmaceutical company, co-promotes INTEGRILIN® (eptifibatid) Injection, a market-leading cardiovascular product, and has a robust clinical development pipeline of product candidates. The Company's research, development and commercialization activities are focused in four disease areas: cardiovascular, oncology, inflammation and metabolic. By applying its knowledge of the human genome, its understanding of disease mechanisms, and its industrialized technology platform, the Company is developing breakthrough personalized medicine products. Headquartered in Cambridge, Mass., the Company also has facilities in South San Francisco, Calif. and Cambridge, UK.

This press release contains "forward-looking statements," including statements about our growth and future operating results, discovery and development of products, potential acquisitions, strategic alliances and intellectual property. Various risks may cause our actual results to differ materially, including: adverse results in our drug discovery and clinical development processes; failure to obtain patent protection for our discoveries; commercial limitations imposed by patents owned or controlled by third parties; our dependence upon strategic alliance partners to develop and commercialize products and services based on our work; difficulties or delays in obtaining regulatory approvals to market products and services resulting from our development efforts; the commercial success of INTEGRILIN® (eptifibatid) Injection; our ability to extinguish the convertible notes assumed in the COR acquisition; and the requirement for substantial funding to conduct research and development and to expand commercialization activities. For a further list and description of the risks and uncertainties we face, see the reports we have filed with the Securities and Exchange Commission. We disclaim any intention or obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

Editors' Note: This release is also available on the Company's website at: www.millennium.com



May 5, 2003

Richard Pazdur M.D., Director
Division of Oncologic Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RECEIVED
MAY 06 2003
CDR/CDER

**RE: VELCADE™ (bortezomib) for Injection
NDA #21-602
Promotional Materials Submission**

Dear Dr. Pazdur:

Enclosed is a desk copy of the promotional materials submitted to the Division of Drug Marketing, Advertising, and Communications for review in anticipation of the accelerated approval of VELCADE (bortezomib) for Injection. Included in the submission are the Press Release and other press kit materials, nursing in-service video and product monograph. We also submitted a peer reviewed manuscript that has not yet been accepted for publication. In addition, we are providing you with a prioritized task list for your reference.

Prioritized Task List

1. Press Release (highest)
2. Press Kit Materials and VNR
3. Sales Aid
4. Launch Ad
5. Enlarged Package Insert
6. Physician Launch Letter
7. Pharmacist Launch Letter
8. Physician Slide Set
9. VELCADE Presentation (A & B)
10. Convention Panel C
11. AHFS Form
12. Peer reviewed Manuscript
13. 3-Screen Animation
14. Reimbursement Materials (brochure, folder, CMS forms)
15. Nurse Q&A Brochure
16. Patient Brochure



Prionitized Task List (continued)

17. Nurse in-service video
18. Dosing Calculator
19. Pens
20. Convention Panel A
21. Convention Panel B
22. VELCADE Exhibit Graphics
23. Mini Visual Aid
24. One-page Launch Ad
25. Portable Exhibit Panels (A, B, C and D)
26. ASCO Abstract Schedule
27. Product Monograph
28. Formulary Kit Housing
29. Post-it Note
30. Adams Reprint
31. Hideshima Reprint
32. Mini-monograph
33. Proteasome Inhibition Animation (lowest)

Provided below is a list of the pieces that are ready for review.

- Enlarged Package Insert (submitted April 9)
- VELCADE Exhibit Graphics (hanging signs) (submitted April 18)
- 3-Screen MOA Animation (submitted April 15)
- Pens A & B (submitted April 18)
- Reimbursement Brochure (submitted April 15)
- Reimbursement Folder (submitted April 15)
- Formulary Kit Housing (submitted April 30)
- Post-it Note (submitted April 18)
- Adams Reprint (submitted April 2)
- Hideshima Reprint (submitted April 2)
- Mini-monograph (submitted April 9)
- Proteasome Inhibition Animation: (submitted April 15)

If you have any questions, please feel free to contact me at 617-551-8951 or via secure e-mail at tlewis@mpi.com.

Sincerely,

Tanya Lewis, M.S.
Sr. Mgr., Worldwide Regulatory Affairs

Enclosures
M-042

Confidential

Millennium Pharmaceuticals, Inc.
 75 Sidney Street
 Cambridge, MA 02139
 Tel 617 679-7000
 mlnm.com



Facsimile Transmittal

TO	Sean Bradley	FAX	(301) 827-4590
FROM	Tanya Lewis	DATE	12 May 2003
RE	Information Request - Phase 4 Commitment Letter		
CC		PAGES	including cover sheet 9
<input checked="" type="checkbox"/> Urgent	<input type="checkbox"/> For Review	<input type="checkbox"/> Please Comment	<input type="checkbox"/> Please Reply <input type="checkbox"/> FYI

MESSAGE:

Sean,

Per your request, attached is our written acceptance of the Phase 4 commitment.

If you have any questions, please contact me at 617-551-8951.

Sincerely,

Tanya Lewis, M.Sc.
 Senior Manager
 World Wide Regulatory Affairs and Pharmacovigilance
 Millennium Pharmaceuticals, Inc.

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.millennium.com

May 12, 2003



Richard Pazdur, M.D.
Director
Division of Oncology Drug Products (HFD-150)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

NDA # 21-602 - VELCADI™ (bortezomib) for Injection
GENERAL CORRESPONDENCE
RE: PHASE 4 COMMITMENT LETTER

Dear Dr. Pazdur:

Attached is the sponsor's agreement to the phase 4 commitments proposed by the Agency.
If you have any questions, please feel free to contact me at 617-551-8951.

Sincerely,

Tanya Lewis, MSc
Senior Manager
Worldwide Regulatory Affairs
Millennium Pharmaceuticals, Inc.

Bradley, Sean

From: Bross, Peter F
Sent: Tuesday, May 06, 2003 11:42 AM
To: 'Lewis, Tanya'
Cc: Bradley, Sean; Pietrusko, Robert
Subject: Velcade Duration of Response

Sensitivity: Confidential

> Here is our response to your e-mail from this weekend. Please let me
> know if you have any questions. We would be happy to have a telephone
> conversation to discuss the information.

Tanya:

We received the information and will forward the info to the statisticians. The ~~datasets~~ datasets did provide information on response duration. It looks to me as though your analysis was for a duration of ~~and~~ and we planned on an analysis of duration of ~~We~~ We have asked our statistician to perform both analyses and we will then make a decision about what to put in the label.

We plan to meet with Dr. Temple late this afternoon after he has reviewed the label and our reviews. I believe Sean has set up a brief telecon tomorrow morning at 8:00 AM to discuss any outstanding issues with label and phase 4.

Thanks,
-Peter

Bradley, Sean

From: Lewis, Tanya [Tanya.Lewis@mpi.com]
Sent: Monday, May 05, 2003 8:53 PM
To: Bross, Peter F
Cc: BradleyS@cder.fda.gov; Pietrusko, Robert; farrella@cder.fda.gov
Subject: Duration of Response: Algorithm II. ~~Documentation~~ Documentation

Importance: High
Sensitivity: Confidential



Duration of ~~Doc~~ mmsalert.txt
ponse Algorithumentation.pdf.

Hi Dr. Bross,

Here is our response to your e-mail from this weekend. Please let me know if you have any questions. We would be happy to have a telephone conversation to discuss the information. Have a good night.

Tanya

**PHASE 4 COMMITMENT LETTER****Clinical Phase 4 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 Therapy"**

The Sponsor agrees to provide complete study reports for the above mentioned studies. A study report will be submitted for study 039 in Q2 2005. A study report will be submitted for study 029 in Q1 2004.

- 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.**

The Sponsor agrees to initiate and complete a study in previously untreated multiple myeloma patients. The study details will be established under special protocol assessment. The Sponsor plans to initiate this study in Q3 2005.

- 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.**

The Sponsor agrees to provide the above mentioned follow up data for studies 025 and 029 in Q1 2004. The data for study 039 will be provided in Q2 2005.



PHASE 4 COMMITMENT LETTER

Non clinical Pharmacology/Toxicology Phase 4 commitments:

Additional non-clinical studies appear warranted given the undefined etiology of cardiovascular effects seen in multiple animal studies, as well as the occurrence of cardiovascular adverse events in patients.

1. The Sponsor should conduct additional investigations of the cardiovascular effects of bortezomib at acutely toxic doses that explore bortezomib induced lethality at 12-14 hours post-dose. Studies should be conducted in a species that most closely models the human response. An investigational study in cynomolgus monkeys would be appropriate, with a focus on potential interventions that could both explore mechanisms of cardiovascular effects and possible clinically relevant interventional therapies. Study protocols may be submitted to the Division for review prior to the conduct of the study.

The Sponsor agrees to conduct a study of cardiovascular effects of bortezomib in cynomolgus monkeys. This study will be completed in Q2 2004.

2. The Sponsor should conduct an additional *in vitro* study in cells transfected with the normal PrP gene to determine if pharmacologically relevant concentrations of bortezomib result in the accumulation of normal, misfolded, or detergent insoluble and proteinase resistant forms of PrP protein in the cytosol, similar to results obtained with other proteasome inhibitors as reported by Ma and Lindquist, 2002. As appropriate, further investigations should be undertaken to understand the implications of any observed effects.

The Sponsor agrees to conduct an *in vitro* study in cells transfected with the normal PrP gene to determine if pharmacologically relevant concentrations of bortezomib result in the accumulation of normal, misfolded, or detergent insoluble and proteinase resistant forms of PrP protein in the cytosol. The Sponsor cannot commit to a completion date at this time because the study described above will not be completely controlled by the Sponsor.

**PHASE 4 COMMITMENT LETTER****Clinical Pharmacology Phase 4 commitments:**

- 1. You should conduct a study to characterize the Pharmacokinetics (PK) of bortezomib as a single agent at 1.3 and 1.0 mg/m² twice weekly 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 cycle to address the time dependent changes in the PK of bortezomib as a single agent.**

The Sponsor agrees to conduct a study to characterize the PK of bortezomib as a single agent at 1.3 and 1.0 mg/m² twice weekly dosing. The protocol will be submitted for Agency review in Q4 2003.

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

The Sponsor agrees to conduct a study with bortezomib in patients with various degrees of liver function. Meetings are ongoing to discuss study design, protocol development, and site selection. A draft protocol will be submitted to the Agency for review in Q4 2003. The start of this study will be determined by CTEP's Organ Dysfunction group. The Sponsor is currently working with CTEP to expedite the start of this study. It is anticipated that this study will take approximately 12 months from initial patient enrollment to completion of the study. A final Clinical Pharmacology Report will be made available within 3 months of clinical study completion.

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

The Sponsor agrees to prepare a Clinical Pharmacology Report in approximately three months after completion of this study in patients with varying degrees of renal dysfunction and submit it for your review. It is the sponsor's understanding that the protocol for this study was submitted by CTEP, changes recommended by the Agency were incorporated and the study is about to commence with investigators in the process of enrolling the initial patients. The projected clinical completion time for this study is Q2 2004. Therefore, it is anticipated that a Clinical Pharmacology report will be available in September 2004.

**PHASE 4 COMMITMENT LETTER**

- 4. We require that you 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. Induction study (RPT-00021) with rifampin as a positive control indicated significant inhibition of CYP 3A4 by bortezomib even at 2.5 μ M concentration. The applicant should reevaluate this difference and conduct an *in vitro* study.**

The Sponsor agrees to conduct a study to evaluate the inhibition potential of bortezomib for CYP 3A4 using human liver microsomes. A protocol will be submitted for Agency review in Q3 2003. The sponsor expects to submit a final report from this study in Q4 03. In addition the Sponsor agrees to perform an *in vitro* study to evaluate the inhibition of CYP 3A4 by bortezomib. A protocol will be submitted to the Agency for review in Q3 2003 and the sponsor expects to submit a final report for this study in Q4 2003.

- 4. 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.**

The Sponsor agrees to conduct a study to evaluate the contribution of cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2 in the metabolism of bortezomib using *in vitro* systems. A protocol for this study will be submitted in Q3 2003. The Sponsor expects to submit a final report for this study in Q4 2003.

- 5. You should conduct a PK and PK/PD (pharmacokinetics/pharmacodynamics) study to examine the potential drug-drug interactions between bortezomib and a drug that is an inhibitor of cytochrome P450 3A4 (e.g., antifungal agents or antibiotics that are potent inhibitors of CYP 3A4). You should also collect the adverse reactions noted in the study and evaluate any relationship between plasma levels and adverse reactions.**

The Sponsor agrees to conduct a drug interaction study with a representative inhibitor of cytochrome P450 3A4. A draft protocol will be submitted for Agency review in Q3 2003.

Document Information Page

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Application #(s):	NDA 21-602
Document Type:	NDA Letter
Document Group:	Miscellaneous/General Correspondence Letters
Document Name:	Letter confirming issues discussed between firm and FDA
Shortcut ID Code:	NDA-K2
COMIS Decision:	AD (ADVICE - CONFIRMATION OF ISSUES DISCUSSED)
COMIS Data Entry:	
Drafted by:	SB/May 20, 2003
Revised by:	
Initialed by:	DPease/05-20-03
Finalized:	SB/May 20, 2003
Filename:	C:\Data\My Documents\My Documents\NDAS\21-602\Velcade\Letters\Phase4Commitments and Dates.doc
DFS Key Words:	
Notes:	
Linking Instructions:	Link the outgoing letter to the incoming document(s) that is the subject of the discussion being confirmed. If there is no applicable incoming document to link to, then link this letter to the original N document.

DP 5-22-03
110 DFS for
FINAL SIGN-OFF

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

DOCUMENT INFORMATION PAGE

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Application #(s): NDA 21-602

Document Type: NDA Letters
Document Group: NDA Approval Letters
Document Name: NDA Accelerated Approval Letter
Shortcut ID Code: NDA-13

COMIS Decision Code: AP

Drafted by: SB/09MAY03
Revised by:
Initialed by: DPease/05-12-03
CLiang/05-13-03
RLostritto/05-13-03
LRosario/05-12-03
DMorse/05-13-02
SAbraham/05-12-03
ARahman/05-12-03
RKane/05-13-03
PBross/05-12-03
AFarrell/05-12-03
GWilliams/05-13-03
RPazdur/05-13-03
Finalized: SB/13MAY03
Filename:

DFS Key Words:

Notes:

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Melody Brown

From: Sean Bradley, CSO

Fax: 617-551-3742

Fax: 310-827-4590

Phone: 617-551-4977

Phone: 301-594-5770

Pages, including cover sheet:

Date: May 1, 2003

Re: NDA 21-602 VELCADE

Urgent For Review Please Comment Please Reply Please Recycle

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Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and have attached comments that will be the basis for our May 2, 2003 CMC discussion.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Regards,

Sean Bradley, R.Ph.


Regulatory Project Manager

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Melody Brown

From: Sean Bradley, CSO

Fax: 617-551-3742

Fax: 310-827-4590

Phone: 617-551-4977

Phone: 301-594-5770

Pages, including cover sheet:

Date: April 23, 2003

Re: NDA 21-602 VELCADE

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Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and have attached deficiency comments relating to the drug product.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Regards,

Sean Bradley, R.Ph.


Regulatory Project Manager

Deficiency comments relating to the drug product:

1. The HPLC chromatography for drug substance (Vol.2, p.144) and drug product (Vol.4, p.181) are identical. Please resolve this discrepancy.
2. 



NDA 21-602

Millennium Pharmaceuticals
75 Sidney St.
Cambridge, MA 02139

Attention: Tanya Lewis, M.S.
Senior Manager, Regulatory Affairs

Dear Ms. Lewis:

Please refer to your new drug application (NDA) for Velcade (bortezomib) for Injection.

We also refer to your submission dated May 12, 2003 and our May 13, 2003 approval letter.

As discussed via teleconference on May 16, 2003 between Tanya Lewis and Sean Bradley of this Division, this letter is an updated version of the Subpart H and Phase 4 Commitments for NDA 21-602.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study commitment(s) specified in your submission dated May 12, 2003. These commitment(s), along with any completion dates agreed upon, are listed below.

Clinical:

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" (This study report will be submitted to the Agency in the second quarter of 2005.)
 - 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" (This study report will be submitted to the Agency in the first quarter of 2004.)
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. (It is anticipated that this study will be initiated in the third quarter of 2005.)

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. (The data for studies 025 and 029 will be submitted to the Agency in the first quarter of 2004. The data for study 039 will be submitted to the Agency in the second quarter of 2005.)

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing study commitment(s) must be clearly designated "Subpart H Postmarketing Study Commitments."

In addition, we note your following postmarketing study commitments, specified in your submission dated May 12, 2003, that are not a condition of the accelerated approval. These commitments are listed below:

Nonclinical Pharmacology/Toxicology:

Additional non-clinical studies are warranted given the undefined etiology of cardiovascular effects seen in multiple animal studies, as well as the occurrence of cardiovascular adverse events in patients.

4. Conduct additional investigations of the cardiovascular effects of bortezomib at acutely toxic doses that explore bortezomib induced lethality at 12–14 hours post-dose. Studies should be conducted in a species that most closely models the human response. An investigational study in cynomolgus monkeys would be appropriate, with a focus on potential interventions that could both explore mechanisms of cardiovascular effects and possible clinically relevant interventional therapies. Study protocols may be submitted to the Division for review prior to the conduct of the study. (This study will be completed in the second quarter of 2004.)

Protocol Submission: Within 3 months of the date of this letter
Study Start: Within 5 months of the date of this letter
Final Report Submission: Within 12 months of the date of this letter

5. Conduct an additional *in vitro* study in mammalian cells transfected with the normal PrP gene to determine if pharmacologically relevant concentrations of bortezomib result in the accumulation of normal, misfolded, or detergent insoluble and proteinase resistant forms of PrP protein in the cytosol, similar to results obtained with other proteasome inhibitors as reported by Ma and Lindquist, 2002. As appropriate, further investigations should be undertaken to understand the implications of any observed effects. (We understand that you cannot commit to a completion date at this time because you will not have complete control over the conduct of the study.)

Protocol Submission: Within 9 months of the date of this letter
Study Start: Within 12 months of the date of this letter
Final Report Submission: Within 24 months of the date of this letter

Clinical Pharmacology and Biopharmaceutics:

6. Conduct a study to characterize the pharmacokinetics (PK) of bortezomib as a single agent at 1.3 and 1.0 mg/m² twice weekly in at least 12 multiple myeloma patients at each dose level. Patients should have normal to mildly decreased creatinine clearance value (≥ 50 mL/min). The pharmacokinetics should be characterized both at Cycle 1 and at a subsequent cycle to address the time dependent changes in the PK of bortezomib as a single agent. (This protocol will be submitted to the Agency for review in the fourth quarter of 2003.)

Protocol Submission: Within 6 months of the date of this letter
Study Start: Within 9 months of the date of this letter
Final Report Submission: Within 22 months of the date of this letter

7. As bortezomib is metabolized and eliminated by the liver, a pharmacokinetic and pharmacokinetic/safety (PK and PK/Safety) study should be conducted in patients with hepatic impairment to provide dosing recommendations for this patient population. (A draft protocol will be submitted to the Agency for review in the fourth quarter of 2003. It is anticipated that this study will take approximately 12 months from initial patient enrollment to completion. A final Clinical Pharmacology report will be made available to the Agency within 3 months of clinical study completion.)

Protocol Submission: Within 6 months of the date of this letter
Study Start: Within 9 months of the date of this letter
Final Report Submission: Within 26 months of the date of this letter

8. Conduct a study to evaluate the PK and PK/Safety of bortezomib in patients with advanced malignancies and varying degrees of renal dysfunction. (The projected clinical completion time for this study is second quarter 2004. Therefore, it is anticipated that the Clinical Pharmacology report will be made available in September 2004.)

Protocol Submission: CTEP Study 5874
Study Start: May 12, 2003
Final Report Submission: Within 16 months of the date of this letter

9. 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 the *in vitro* study, you may need to conduct a clinical drug interaction study to evaluate the interaction between bortezomib and midazolam or other CYP 3A4 substrate. (The protocol for the study to evaluate the inhibition potential of bortezomib for CYP 3A4 using human liver microsomes will be submitted to the Agency for review in the third quarter of 2003. It is anticipated that the final report will be submitted to the Agency in the fourth quarter of 2003. The protocol for the *in vitro* study to evaluate the inhibition of CYP 3A4 by bortezomib will be submitted to the Agency for review in the third quarter of 2003. It is anticipated that the final study report will be submitted to the Agency in the fourth quarter of 2003.)

Protocol Submission: Within 1 months of the date of this letter
Study Start: Within 3 months of the date of this letter
Final Report Submission: Within 6 months of the date of this letter

10. 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. (A protocol for this study will be submitted in the third quarter of 2003. It is anticipated that the final study report will be submitted in the fourth quarter of 2003.)

Protocol Submission: Within 1 months of the date of this letter
Study Start: Within 3 months of the date of this letter
Final Report Submission: Within 6 months of the date of this letter

11. Conduct a PK and PK/PD (pharmacokinetics/pharmacodynamics) study to examine the potential drug-drug interactions between bortezomib and a drug that is an of cytochrome P450 3A4 inhibitor (e.g., antifungal agents or antibiotics that are potent inhibitors of CYP 3A4). You should also collect the adverse reactions noted in the study and evaluate any relationship between plasma levels and adverse reactions. (The draft protocol for this study will be submitted to the Agency for review in the third quarter of 2003.)

Protocol Submission: Within 6 months of the date of this letter
Study Start: Within 10 months of the date of this letter
Final Report Submission: Within 25 months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

If you have any questions, call Sean Bradley, Regulatory Project Manager, at 301-594-5770.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	From: Sean Bradley, CSO
Fax: 617-551-3742	Fax: 301-827-4590
Phone: 617-551-8951	Phone: 301-594-5770
Pages, including cover sheet: 4	Date: May 6, 2003
Re: NDA 21602/Velcade Phase 4 commitments	

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Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

Attached are the Agency's phase 4 commitment comments which we will be discussing tomorrow morning.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/s/
Regulatory Project Manager

The following are Clinical Phase 4 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 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.

The following are non-clinical Pharmacology/Toxicology phase 4 commitments:

1. Additional non-clinical studies appear warranted given the undefined etiology of the cardiovascular effects seen in multiple animal studies, as well as the occurrence of cardiovascular adverse events in patients.
 - Given the narrow safety margin between the recommended clinical dose (1.3 mg/m²) and 100 % lethality in non-clinical studies (3.0 mg/m² in monkeys), we recommend the sponsor determine the factors associated with PS-341 induced lethality at 12–14 hours post-dose.
 - Since PS-341 promotes dissimilar effects in monkey and mouse, future studies should be conducted in a species that most closely models the human response.
 - The Sponsor should identify the cardiac cell type(s) that are most effected following PS-341 administration to provide potential clinical interventions in the event of an overdose.
 - Future non-clinical studies need to incorporate neuronal assessments to identify or rule out CNS involvement in these phenomena.
2. The Sponsor should conduct a study in cells transfected with a normal PrP gene to determine if administration of PS-341 results in the accumulation of proteins in the cytosol, similar to treatment with other proteasome inhibitors such as lactacystin or epoxomicin, as reported by Ma and Lindquist, 2002. Further, determine if misfolding of the normal PrP protein occurred with the formation of proteins with a PrP^{sc}-like conformation. The implications of these findings to the possible initiation and/or exacerbation of spongiform encephalopathies should be addressed.

Clinical Pharmacology phase 4 commitments:

- 1) You should conduct a study to characterize the Pharmacokinetics (PK) of bortezomib as a single agent at 1.3 and 1.0 mg/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) As bortezomib is metabolized by the liver, you should conduct a pharmacokinetic and pharmacokinetic/safety (PK and PK/Safety) study in patients with hepatic impairment to adequately provide dosing recommendations for this special patient population in the labeling for VELCADE.
- 3) You should conduct a study to evaluate the PK and PK/safety of bortezomib in patients with advanced malignancies and varying degrees of renal dysfunction.
- 4) You should conduct PK and PK/PD (pharmacokinetics/pharmacodynamics) studies to examine the potential for drug-drug interactions between bortezomib and drugs that are inhibitors (e.g., ketoconazole), or inducers (e. g., rifampin) of cytochrome P450 3A4. You should also collect adverse reactions noted in this study and evaluate any relationship between plasma levels and adverse reactions.
- 5) You should evaluate the contribution of cytochrome P 450 3A4, 2D6, 2C19, 2C9, and 1A2 in the metabolism of bortezomib using in vitro systems (microsomes, hepatocytes, liver tissue, etc.) Based on the results of the study, additional drug-drug interaction studies may be required.

Please submit the proposed study protocols for Agency review.

Phase 4 Studies requested but not required:

- 1) Provide the complete study report, pharmacogenomic data, and data analysis collected in study 025.
- 2) Consider changing the single dose vial size to minimize chance for overdose by reducing the contents to a maximum of 3.0 mg. (This represents the actual dose for a 2.30 m² person dosed at 1.3 mg/m² or a 2.0 m² person dosed at 1.5 mg/m².)
- 3) Velcade appears to be more tolerable at 1.0 mg/m² compared with 1.3 mg/m² and there is not sufficient information on efficacy to determine a dose-response. Provide additional information on the safety and efficacy of Velcade at a different dose, for example 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.

*** TX REPORT ***

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Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	From: Sean Bradley, CSO
Fax: 617-551-3742	Fax: 301-827-4590
Phone: 617-551-8951	Phone: 301-594-5770
Pages, including cover sheet: 4	Date: May 6, 2003
Re: NDA 21602/Velcade Phase 4 commitments	

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Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

Attached are the Agency's phase 4 commitment comments which we will be discussing tomorrow morning.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

*** TX REPORT ***

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Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Melody Brown

From: Sean Bradley, CSO

Fax: 617-551-3742

Fax: 310-827-4590

Phone: 617-551-4977

Phone: 301-594-5770

Pages, including cover sheet

Date: May 1, 2003

Re: NDA 21-602 VELCADE

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We are currently reviewing your application and have attached comments that will be the basis for our May 2, 2003 CMC discussion.

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From: Sean Bradley, CSO

Fax: 617-551-3742

Fax: 310-827-4590

Phone: 617-551-8951

Phone: 301-594-5770

Pages, including cover sheet: 2

Date: April 30, 2003

Re: NDA 21-602 VELCADE

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We are currently reviewing your application and request the following information that is needed to continue our review.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/s/
Regulatory Project Manager

Please send a list of the ongoing/planned investigations in multiple myeloma as stated in your NDA presentation. Has any protocols been submitted to the FDA and if so under what IND?

*** TX REPORT ***

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SUBADDRESS
CONNECTION ID MILLENNIUM INC.
ST. TIME 04/30 08:52
USAGE T 00'35
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Fax



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Center for Drug Evaluation and Research, HFD-150
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From: Sean Bradley, CSO

Fax: 617-551-3742

Fax: 310-827-4590

Phone: 617-551-8951

Phone: 301-594-5770

Pages, including cover sheet: 2

Date: April 30, 2003

Re: NDA 21-602 VELCADE

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From: Sean Bradley, CSO

Fax: 617-551-3742

Fax: 310-827-4590

Phone: 617-551-8951

Phone: 301-594-5770

Pages, including cover sheet: 2

Date: April 28, 2003 (b)

Re: NDA 21-602 VELCADE/Labeling

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Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and request the following information that is needed to continue our review.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R Ph

/s/
Regulatory Project Manager

In order to consider the proposed label changes for the mechanism of action section of the Velcade label we will need annotations for the following statements:

Mechanism of Action

□

and

□

*** TX REPORT ***

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CONNECTION TEL 916175513742
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Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS

From: Sean Bradley, CSO

Fax: 617-551-3742

Fax: 310-827-4590

Phone: 617-551-8951

Phone: 301-594-5770

Pages, including cover sheet: 2

Date: April 28, 2003 (b)

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FDA Question

In order to consider the proposed label changes for the mechanism of action section of the VELCADE label we will need annotations for the following statements:

Mechanism of Action

Sponsor Response:

An annotated draft package insert was submitted in the Prescribing Information Folder contained in Module 1 of the NDA. A discussion of the data which supports the statements mentioned above is included in the Pharmacology Summary, section 2.6.2.2.4, *In Vitro* Pharmacology of PS-341, Table 2.6.2-2. Links are provided to each reference from this table. The following references were included in the NDA to support the statement that _____

_____ References 3, 5 and 8 are supportive of bortezomib in particular, while the other references support the differential sensitivity of normal and cancer cells to proteasome inhibition in general. Reference 3 below supports the statement that _____

1. An B, Goldfarb RH, Siman R, Dou QP. Novel depeptidyl proteasome inhibitors overcome Bcl-2 protective function and selectively accumulate the cyclin-dependent kinase inhibitor p27 and induce apoptosis in transformed, but not normal human fibroblasts. *Cell Death Differentiation* 1198; 5 (12):1062-75.
2. Chen C, Lin H, Karanes C, Pettit GR, Chen BD. Human THP-1 monocytic leukemic cells induced to undergo monocytic differentiation by bryostatin 1 are refractory to proteasome inhibitor-induced apoptosis. *Cancer Research* 2000; 60 (16):4377-85.
3. Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Research* 2001; 61 (7):3071-6.

4. Kudo Y, Takata T, Ogawa I, Kaneda T, Sato S, Takekoshi T et al. p27Kip1 accumulation by inhibition of proteasome function induces apoptosis in oral squamous cell carcinoma cells. *Clinical Cancer Research* 2000; 6 (3): 916-23.
5. Ma MH, Parker K, Manyak S, Yang H, M. FJ, Altamirano C et al: The Proteasome Inhibitor PS-341 Markedly Enhances Sensitivity Of Multiple Myeloma Tumor Cells To Chemotherapeutic Agents. *Clinical Cancer Research*; In press.
6. Masdehors P, Merle-Beral H, Magdelenat H, Delic J. Ubiquitin-proteasome system and increased sensitivity of B-CLL lymphocytes to apoptotic death activation. *Leukemia & Lymphoma* 2000; 38 (5-6):499-504.
7. Orłowski RZ, Eswara JR, Lafond-Walker A, Grever MR, Orłowski M, Dang CV. Tumor growth inhibition induced in a murine model of human Burkitt's lymphoma by a proteasome inhibitor. *Cancer Research* 1998; 58 (19):4342-8.
8. Soengas MS, Steiner P, Ray S, Zilfou JT, Mosher R, Fernandez Y et al. Bypassing Cell Death Deficiencies in Human Melanoma (Abstract). *Cancer Genetics and Tumor Suppressor Genes*, 2002; Cold Spring Harbor, NY. Cold Spring Harbor Laboratory. Abstract 238.

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Sean Bradley, R.Ph.


Regulatory Project Manager

Old (Lines 523-524) :

New (Lines 530-531):

Justification:

Old (Lines 525-527):

New (Lines 532-534):

Justification:

Question: Can you provide any data to suggest that the reconstituted drug product will not support microbial growth?

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We are currently reviewing your application and request the following information that is needed to continue our review.

If you have any questions please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Reference is made to NDA 21-602 and to FDA fax (S. Bradley, FDA to T. Lewis, Millennium, dated April 28, 2003). Please find Millennium's response to FDA question below.

FDA Question: Can you provide any data to suggest that the reconstituted drug product will not support microbial growth?

Sponsor Response: We can not provide any data on microbial growth in the reconstituted solution. The reconstituted stability studies did not include testing for microbial contamination. The eight hour use period requested on the Velcade for Injection reconstituted product is based on the chemical stability data provided in the application (Section 3.2.P.8.3.6, Table 4). As stated on the product label, Velcade for Injection is provided as a "single use vial" for reconstitution. In addition, the package insert contains the appropriate wording to assure that aseptic techniques are used when preparing the product for injection. (Refer to the following sections of the Package Insert; *Administration Precautions, Reconstitution/Preparation for Intravenous Administration and Stability.*)

Lastly, it is our understanding from our research of other oncology products which are unpreserved and reconstituted with unpreserved diluents in single use vials, that it is standard practice to allow a use period of anywhere from eight to twenty four hours after reconstitution. We found several of these products listed in the Physician's Desk Reference (PDR). In addition, we are requesting this additional use time (eight hours versus four hours) to provide the necessary flexibility to the hospital pharmacies and to eliminate unnecessary waste of the product.

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Re: NDA 21-602 VELCADE/Labeling

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Attached is the FDA-revised version of the product labeling for your review.

There have been significant changes to the label for the following reasons:

- 1) We do not allow secondary analyses or endpoints in the label.
- 2) We cannot discuss combination therapy because to mention combination therapy, we would be implying an indication (e.g., the combination of Velcade plus dexamethasone). For an indication, the study(ies) of Velcade plus dexamethasone would have to be adequate and well-controlled (i.e., randomized, controlled, and with appropriate choice of endpoints).
- 3) We did not agree on the response rates because our analysis excluded the following patients:
 - a) Three patients who received biacin/steroid after having received steroids as the first line therapy after consultation with ODAC about whether these patients had been maximally treated. (Thus 1 CR (Blade) patient was excluded).
 - b) The CR (Blade) patient who did not have a confirmatory negative immunofixation as required by the study could not be labeled as CR (Blade). However, this patient was included as a responder in the other efficacy categories.
- 4) We did not have the report for study 029.

An electronic copy of the FDA-proposed labeling will also be forwarded to you.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

151
Regulatory Project Manager

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