

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION <b>INVESTIGATIONAL NEW DRUG APPLICATION (IND)</b> <i>(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)</i>		Form Approved: OMB No. 0910-0430. Expiration Date: April 30, 2009 See OMB Statement on Reverse. <b>Note:</b> No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).
1. NAME OF SPONSOR <b>Division of Cancer Treatment and Diagnosis</b>		2. DATE OF SUBMISSION <b>06/15/2010</b>
3. ADDRESS (Number, Street, City, State and Zip Code) <b>Executive Plaza North, Suite 7111          6130 Executive Boulevard, MSC 7428          National Institutes of Health, DCTD, NCI          Bethesda, MD 20892-7428</b>		4. TELEPHONE NUMBER (Include Area Code) <b>(301) 496-7912</b>
5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code) <b>PS-341</b>		6. IND NUMBER (If previously assigned) <b>58443</b>
7. INDICATION(S) (Covered by this submission) <b>Cancer</b>		
8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: <input type="checkbox"/> PHASE 1 <input type="checkbox"/> PHASE 2 <input type="checkbox"/> PHASE 3 <input type="checkbox"/> OTHER _____ (Specify)		
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR Part 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.		
<b>10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.</b>		SERIAL NUMBER <b>0738</b>
11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply) <input type="checkbox"/> INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) <input type="checkbox"/> RESPONSE TO CLINICAL HOLD PROTOCOL AMENDMENT(S):      INFORMATION AMENDMENT(S):      IND SAFETY REPORT(S): <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> CHEMISTRY/MICROBIOLOGY <input type="checkbox"/> INITIAL WRITTEN REPORT <input type="checkbox"/> CHANGE IN PROTOCOL <input type="checkbox"/> PHARMACOLOGY/TOXICOLOGY <input checked="" type="checkbox"/> FOLLOW-UP TO A WRITTEN REPORT <input type="checkbox"/> NEW INVESTIGATOR <input type="checkbox"/> CLINICAL <input type="checkbox"/> RESPONSE TO FDA REQUEST FOR INFORMATION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> GENERAL CORRESPONDENCE <input type="checkbox"/> REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN INACTIVATED, TERMINATED OR DISCONTINUED <input type="checkbox"/> OTHER _____ (Specify)		
<b>CHECK ONLY IF APPLICABLE</b>		
<b>JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.</b>		
<input type="checkbox"/> TREATMENT IND 21 CFR 312.35(b) <input type="checkbox"/> TREATMENT PROTOCOL 21 CFR 312.35(a) <input type="checkbox"/> CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)		
<b>FOR FDA USE ONLY</b>		
CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

**CONTENTS OF APPLICATION**

12.

This application contains the following items: (Check all that apply)

- 1. Form FDA 1571 [21 CFR 312.23(a)(1)]
- 2. Table of Contents [21 CFR 312.23(a)(2)]
- 3. Introductory statement [21 CFR 312.23(a)(3)]
- 4. General Investigational plan [21 CFR 312.23(a)(3)]
- 5. Investigator's brochure [21 CFR 312.23(a)(5)]
- 6. Protocol(s) [21 CFR 312.23(a)(6)]
  - a. Study protocol(s) [21 CFR 312.23(a)(6)]
  - b. Investigator data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - c. Facilities data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - d. Institutional Review Board data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- 7. Chemistry, manufacturing, and control data [21 CFR 312.23(a)(7)]
  - Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]
- 8. Pharmacology and toxicology data [21 CFR 312.23(a)(8)]
- 9. Previous human experience [21 CFR 312.23(a)(9)]
- 10. Additional information [21 CFR 312.23(a)(10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION?  YES  NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION?  YES  NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.


14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

**Joan Mauer, Chief, Clinical Trials Monitoring Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI**

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

**James Zwiebel, M.D., Chief, Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI**

**I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.**

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE  <b>Jan Casadei, Ph.D., Chief, Regulatory Affairs Branch</b>	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE  	
18. ADDRESS (Number, Street, City, State and Zip Code) <b>Executive Plaza North, Suite 7111 6130 Executive Boulevard, MSC 7428 National Institutes of Health, DCTD, NCI Bethesda, MD 20892-7428</b>	19. TELEPHONE NUMBER (Include Area Code) <b>(301) 496-7912</b>	20. DATE <b>06/15/2010</b>

**(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)**

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Amundale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448	"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."
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Please **DO NOT RETURN** this application to this address.



DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health  
National Cancer Institute

## Memorandum

DATE: June 14, 2010

FROM: Jan Casadei, Ph.D., Regulatory Affairs Branch, CTEP, DCTD, NCI  
EPN/ Suite 7111

SUBJECT: **Follow-Up Written Report** for IND 58443: PS-341 (bortezomib; Velcade)  
NCI Protocol # CALGB-140502

TO: Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA

FDA FAX #: 301-796-9845

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Reference is made to the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), Investigational New Drug Application (IND) for IND 58443: PS-341 (bortezomib; Velcade).

Enclosed is the **Follow-Up Written Report**. This report will be distributed to investigators.

If upon further investigation relevant information becomes available, then we will submit a follow-up written report. This follow-up report will also be distributed to investigators.

All information included in this IND and all information contained therein is considered **CONFIDENTIAL AND PROPRIETARY** and shall not be released to any other parties without the expressed written consent of the DCTD, NCI. The legal protection of such confidential material is hereby claimed under applicable provisions of 21 CFR 312.130.

Enclosures

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**IND SAFETY REPORT: FOLLOW-UP #1**TO: *Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA*

FAX: 301-796-9845

1. IND NUMBER  
584432. AGENT NAME  
PS-341 (bortezomib; Velcade)3. DATE  
**June 14, 2010**4. SPONSOR  
Division of Cancer Treatment and Diagnosis, National Cancer Institute5. REPORTER=S NAME, TITLE, AND INSTITUTION  
John Wright, MD, Ph.D. – Associate Branch Chief for Investigational Therapeutics 2,  
Investigational Drug Branch, CTEP, DCTD, NCI6. PHONE NUMBER  
301-496-11967. FAX NUMBER  
301-402-04288. PROTOCOL NUMBER (AE #)  
CALGB-10502 (AE# 1887123)9. PATIENT IDENTIFICATION  
11611710. AGE  
7311. SEX  
Female

## 12. DESCRIPTION OF ADVERSE EVENT

The patient was a 73-year-old female with acute myeloid leukemia who experienced grade 5 left ventricular diastolic dysfunction while on a phase 2 study using the investigational agent bortezomib in combination with daunorubicin and cytarabine. She began the first course of the remission induction therapy on June 1, 2009, and she received the last dose of bortezomib on June 11, 2009 (Cycle 1, Day 11). On June 5, 2009 (Cycle 1, Day 5), the patient developed dyspnea with an oxygen saturation of 88% on room air. The patient was placed on a 100% non-rebreather mask and placed on Lasix<sup>®</sup>. On June 6, 2009 (Cycle 1, Day 6), the patient had a potassium level of 2.3 mmol/L (reference range: 3.5-5.1 mmol/L); she received supplemental potassium, and on June 9, 2009, the potassium level was within normal range. On June 13, 2009, the patient experienced a change in mental status. She was able to follow simple commands but was somnolent. The blood pressure was 181/100 mmHg, and Vasotec<sup>®</sup> was administered. A CT scan of the brain was performed and showed a new right sylvian subarachnoid hemorrhage. Bilateral parietal occipital lucencies suggested hypertensive encephalopathy. The patient was transferred to the MICU for monitoring and was placed on a Cardene<sup>®</sup> drip to control the hypertension. On June 19, 2009, the patient was alert, oriented and able to move all extremities. A chest X-ray revealed pulmonary edema. The physical examination revealed frothy, bloody secretions and congestion throughout bilateral lungs fields. She was placed on a bipap machine and later intubated. On June 22, 2009, the patient became hypotensive and was placed on vasopressors. The neurologic examination revealed fixed and dilated pupils. On June 24, 2009, her medications were discontinued, and the patient expired on the same day. Additional information has been requested. There is a reasonable possibility that the experience may have been caused by the drug.

## 13. DOSE, ROUTE, AND SCHEDULE

Remission Induction Therapy

Bortezomib 1.3 mg/m<sup>2</sup> IVB over 3-5 seconds on Days 1, 4, 8, and 11

## 14. DATES OF TREATMENT

The patient began the investigational therapy on June 1, 2009, and received the last dose of bortezomib on June 11, 2009 (Cycle 1, Day 11).

## 15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bortezomib = 2891.

There have been two other cases of left ventricular diastolic dysfunction reported to the NCI through AdeERS as serious adverse events for PS-341.

## 16. COMMENTS

The following was also administered on this protocol:

Daunorubicin: 60 mg/m<sup>2</sup> IV on Days 1-3Cytarabine: 100 mg/m<sup>2</sup> IV CIV on Days 1-7**FOLLOW-UP: BASED UPON FURTHER INVESTIGATION, THIS ADVERSE EVENT IS CONSIDERED UNRELATED TO THE INVESTIGATIONAL AGENT/THERAPY.**

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