

IND SAFETY REPORT: INITIAL WRITTEN REPORT

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

FAX: 301-796-9845

1. IND NUMBER 58443	2. AGENT NAME PS-341 (bortezomib; Velcade)	3. DATE November 4, 2009
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4. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER-S NAME, TITLE, AND INSTITUTION John Wright, MD, PhD – Associate Branch Chief for Investigational Therapeutics 2, Investigational Drug Branch, CTEP, DCTD, NCI	6. PHONE NUMBER 301-496-1196
	7. FAX NUMBER 301-402-0428

8. PROTOCOL NUMBER (AE #)
AAML07P1 (AE# 1850085)

9. PATIENT IDENTIFICATION 792104	10. AGE 6	11. SEX Male
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12. DESCRIPTION OF ADVERSE EVENT
The patient was a 6-year-old male with acute myeloid leukemia who experienced grade 5 left ventricular systolic dysfunction while on a phase 2 study using the investigational agent bortezomib in combination with cytarabine IT, idarubicin and cytarabine. On June 6, 2009, an echocardiogram showed his left ventricular ejection fraction (LVEF) to be at 75%. His LVEF had dropped to 50% when he began the first course of the investigational therapy on August 6, 2009. He received his only dose of cytarabine IT on August 6, 2009 (Cycle 1, Day 1), and the last doses of idarubicin on August 9, 2009 (Cycle 1, Day 4), cytarabine on August 13, 2009 (Cycle 1, Day 8), and bortezomib on August 14, 2009 (Cycle 1, Day 9). On September 3, 2009 (Cycle 1, Day 29), his LVEF was at 30% with an increased resting heart rate of 184 bpm. The patient was started on milrinone. By September 7, 2009 (Cycle 1, Day 33) his LVEF had dropped to 19%. Overall, the patient's prognosis remained poor, and it was suspected that there could be a potentially irreversible heart failure of unclear and possibly multifactorial etiology. His cardiac troponin levels remained elevated and indicative of an ongoing myocardial damage, and his BNP levels were too high to quantitate. His LVEF was at 5% on September 15, 2009 (Cycle 1, Day 41). During the course of his hospitalization, the patient developed a Vancomycin-resistant *enterococci* (VRE) bacteremia with persistent fevers of 105°F and a pancytopenia. The patient's cardiac status continued to worsen and on September 18, 2009 (Cycle 1, Day 44), the patient expired. 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
Cycle = 28 days
Bortezomib 1.3 mg/m² IVP on Days 1, 4 and 8

14. DATES OF TREATMENT
The patient began the investigational therapy on August 6, 2009, and received the last dose of bortezomib on August 14, 2009 (Cycle 1, Day 9).

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using bortezomib = 2964.
There have been 16 other cases of left ventricular systolic dysfunction reported to the NCI through AdEERS as serious adverse events for bortezomib.

16. COMMENTS
The following were also administered on this protocol:
Cytarabine IT: 30-70 mg/m² (age-based dosing) on Day 0
Idarubicin: 12 mg/m² IV over 15 minutes on Days 1-3
Cytarabine: 100 mg/m²/day CIV on Days 1-7

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32(d)(2).

DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.