



DATE: May 24, 2010

FROM: Alice Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI *AP b-MLP JW*

SUBJECT: 17-Allylaminogeldanamycin (17-AAG) and PS-341 (bortezomib; Velcade®) NCI IND Safety Report, AE# 1658762

TO: Investigators Using 17-AAG (NSC 330507) and Bortezomib (NSC 681239)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agents 17-AAG and bortezomib.

The following must be completed by all investigators using 17-AAG, NCI IND 57966, and bortezomib under NCI IND 58443:

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under INDs 57966 or 58443, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with 17-AAG and bortezomib, there does not appear to be a change in the risk-benefit ratio for 17-AAG and bortezomib studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol (s).

The attached Adverse Events Assessment describes the adverse event (s) (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 57-year-old female with colon cancer metastatic to the liver experienced a grade 3 third degree atrioventricular (AV) block while on a phase 1 trial utilizing the investigational agents 17-AAG and bortezomib.

ADVERSE EVENTS ASSESSMENT

IND 57966	58443	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 3: Conduction abnormality/atrioventricular heart block: AV Block-Third degree (Complete AV block)
NSC 330507	681239	
17- Allylaminogeldanamycin (17-AAG)	PS-341 (bortezomib; Velcade®)	
AE: 1658762		Protocol: 6121

The patient is a 57-year-old female with colon cancer metastatic to the liver who experienced a third degree atrioventricular (AV) block while on a phase 1 trial utilizing the investigational agents 17-AAG and bortezomib. She began the first course of the investigational therapy on November 3, 2009, receiving 17-AAG 250 mg/m² IV over 1-2 hours on Days 1, 4, 8, and 11, and bortezomib 1 mg/m² IV push over 3-5 seconds on Days 1, 4, 8, and 11, every 21 days. The patient received the last doses of 17-AAG and bortezomib on December 4, 2009 (Cycle 2, Day 11).

The patient was diagnosed with metastatic colon cancer in December 2007, and is status post multiple-agent systemic chemotherapy. The patient began the investigational therapy on November 3, 2009.

On December 14, 2009 (Cycle 2, Day 21), the patient presented to the clinic for a follow-up visit complaining of weakness, dizziness (also described as lightheadedness with a near syncopal feeling), shortness of breath, and chest tightness which had developed a few days prior. Cardiovascular examination revealed profound bradycardia and 1/6 systolic murmur. The patient, who has no known history of coronary artery disease, was removed from the study and transferred to the ER. She was alert and oriented and afebrile; her vitals were as follows: heart rate, 36 bpm; respiration, 18 breaths per minute; blood pressure, 156/91 mmHg; and oxygen saturation, 98% on room air. An ECG revealed complete heart block with AV dissociation and junctional escape rhythm at 36 bpm, incomplete right bundle branch block, a prolonged QTc interval of 475 ms, possible right ventricular hypertrophy, and ST/T-wave abnormalities suggestive of an inferior infarct. The chest X-ray was unremarkable. Cardiac enzymes were within normal limits. The patient was given a bolus of IV fluids, started on supplemental oxygen, and admitted to the cardiology service. A dual-chamber permanent pacemaker was successfully implanted after which the patient reported a marked improvement in her symptoms.

On December 15, 2009, an echocardiogram revealed mild bi-atrial enlargement and an ejection fraction of 58%. The ECG showed a paced rhythm, and the pacemaker interrogation indicated sinus rhythm at 66 bpm. The patient was discharged home with instructions on activity restrictions and to follow-up with the pace maker clinic on December 23, 2009.

Pacemaker interrogation on January 13, 2010, revealed no complications and a normal pacemaker function. The next pacemaker assessment was scheduled for April 14, 2010.

The patient's past medical/surgical history was remarkable for diabetes mellitus, diabetic neuropathy, and hypertension. Medications taken at the time of the event included amlodipine, aspirin, atorvastatin, Colace®, gabapentin, glyburide, Lantus® insulin, lisinopril, lorazepam, multivitamin, Bactroban®, Percocet®, pioglitazone, and prochlorperazine.

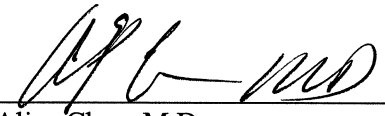
There have been no other cases of third degree AV block reported as serious adverse events through AdEERS under the bortezomib NSC and/or IND, and no other cases of third degree AV block reported as serious adverse events through AdEERS under the 17-AAG NSC and/or IND.

A total of 714 patients have been enrolled in NCI-sponsored clinical trials under the 17-AAG IND and/or NSC, and a total of 3,138 patients have been enrolled in NCI-sponsored clinical trials under the bortezomib IND and/or NSC.

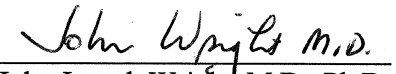
In this case, it is felt that a probable causal relationship exist between the event and 17-AAG.

	AV Block-Third degree
17-AAG	Probable
Bortezomib	Unlikely
Colon cancer	Unlikely

Date: 5/24/10

Signature: 
Alice Chen, M.D.
(IDB Monitor for 17-AAG)

Date: 6/30/10


John Joseph Wright, M.D., Ph.D.
(IDB Monitor for bortezomib)

If this assessment is changed, we will notify your office.

cc: David Berman, M.D., Ph.D.
Worldwide safety: worldwide.safety@bms.com
Bristol-Myers Squibb

Barbara Franklin
Linda Morse
CTEPupdates@mpi.com
Adverse Event Reporting: productsafety@mpi.com
Millennium Pharmaceuticals Inc.