DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ronald Bukowski, M.D.
28099 Gates Mills Blvd.
Pepper Pike, OH 44124

Ref#: 09-HFD-45-03-02

Dear Dr. Bukowski:

Between August 4 and September 15, 2008, Mr. Benjamin Dastoli, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (Protocol (b) (4) entitled "A Phase II, Multicenter, Randomized, Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of (b) (4)) in Combination with (b) (4) Versus (b) (4) Alone for Treatment of (b) (4) Carcinoma") of the investigational drugs (b) (4) performed for (b) (4) .

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

The FDA notes that during the time period between the IRB's approval of the study on April 6, 2004 and closure of the study with the IRB on January 31, 2007, you served as the clinical investigator of this study and that Dr. (b) (6) served as the sub-investigator. As you had retired from your position in January 2008, we note that the FDA inspection of this study was thus facilitated by Dr. (b) (6) .

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. We are aware that at the conclusion of the inspection, Mr. Benjamin Dastoli presented and discussed with your sub-investigator, Dr. (b) (6) , a Form FDA 483, Inspectional Observations. We note

that a copy of the Form FDA 483 was mailed to you at the conclusion of the inspection. We wish to emphasize the following:

1. You failed to obtain the informed consent of each human subject in accordance with 21 CFR part 50 [21 CFR 312.60].

FDA's regulations at 21 CFR 50.20 specify that an investigator shall seek informed consent only under circumstances that provide the prospective subject or the subject's representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. Section 50.25(a) states that in seeking informed consent, certain information shall be provided to each subject, including a description of any reasonably foreseeable risks or discomforts to the subject. [21 CFR 50.25(a)(2)]

a. Per the letter dated July 14, 2004, sent by your site to the IRB, you provided information that the use of [redacted] was associated with the risk of "serious confusion" that had been identified in 23 other individuals, and that based on this possible serious adverse event, the informed consent document was being revised. We note that following notification of the IRB's approval of this revised consent form in a July 27, 2004 letter, your site failed to re-consent the 6 subjects (i.e. Subject # 23240, 23241, 23242, 23243, 23244, 23245) who were enrolled prior to the date of the approval of the revised informed consent document and who were still participating in the study. As a result of this failure, those subjects were not provided with an adequate description of the reasonably foreseeable risks of participating in the study.

b. Per the letter dated August 20, 2004, your site provided information to the IRB that the consent form was being revised to include, among other items, the risk of thromboembolic events. In a letter dated September 20, 2004, the IRB informed you that the revised consent form was approved and that you were required to have previously enrolled subjects sign and date the revised consent form in order to allow their continued participation in the study. We note that following notification of the IRB's approval of this revised consent form, your site failed to re-consent the 9 subjects who were already enrolled (i.e. Subject # 23240, 23241, 23243, 23244, 23246, 23247, 23248, 23249, and 23250) using the approved revised consent form. As a result of this failure, those subjects were not provided with an adequate description of the reasonably foreseeable risks of participating in the study.

c. Per Protocol Amendment #4's summary page, the primary purpose of this amendment was to modify the study treatment after the landmark analysis, which suggested that the addition of [redacted] (b) (4) to [redacted] (b) (4) resulted in progression-free survival and response rates similar to those achieved with [redacted] (b) (4) alone. The revised informed consent form for this amendment, which included information related to the landmark analysis, also included information related to additional risks to the subjects who opted to remain on [redacted], including fatal lung injury, disorders of blood cells, and interaction of

certain food with [redacted]. In a letter dated February 3, 2006, the IRB informed you that the revised consent form was approved and that you were required to have previously enrolled subjects sign and date the revised consent form in order to allow their continued participation in the study. We note that subsequent to the date of the IRB's approval of this revised consent form, your site failed to re-consent Subject #23247 using the approved revised consent form. As a result of this failure, that subject was not provided with an adequate description of the reasonably foreseeable risks of participating in the study.

2. You failed to conduct the study or ensure it was conducted according to the investigational plan [21 CFR 312.60].

a. Protocol Amendment #1 which was in effect during the time of Subject 23241's enrollment into the study, specified that to be included in the study, the subject was to have histologically confirmed [redacted] carcinoma of [redacted]. Per the surgical pathology report dated April 17, 2001, the subject had been diagnosed with [redacted] carcinoma with both [redacted] cell features, and thus the subject did not meet the inclusion criterion for enrollment into the study. However, the subject was enrolled into the study and was administered study medication prior to your site requesting and receiving a waiver from the sponsor that allowed the subject's enrollment in the study.

b. The original protocol and protocol amendments all specified that as a part of the safety plan of the study, enrolled subjects were to be carefully monitored during the entire treatment phase and that safety evaluations which consisted of medical interviews, recording of adverse events, physical examinations, and blood pressure and laboratory measurements, were to be performed on subjects at specified visits throughout the study. With respect to the physical exams, the protocol specified that at the screening and termination visits, the subjects were to have a complete physical exam, and during the treatment phase the subjects were to have limited physical exams every two weeks until 52 weeks into the study and then every 4 weeks thereafter. The protocols also specified that a urinalysis and urine protein/creatinine ratio were to be performed at the screening visit, every 6 weeks during the study, and at the treatment termination visit. Based on the results of the urinalysis and urine protein/creatinine results, the protocols further specified that the subject's dose was to be modified and/or the subject was to have additional testing or adequate follow up subsequent to the termination visit. The protocols further specified that the results from the screening urinalysis would exclude subjects if a specific level of protein in the urine was reached.

In FDA's review of 12 of 12 subject records, there were numerous study visits where your site's records do not indicate that your site conducted the protocol specified physical exams and at either the screening visit, during study treatment visits, and/or termination visits, failed to obtain a urinalysis and/or perform a urine protein/creatinine ratio. In addition, in review of your site's records, documentation could not be found to verify comments made in the CRF

that a physical exam was done. Examples include but were not limited to the following:

Subject #	**Study procedure not conducted or no evidence found to show it was conducted**	**Study visit the procedure was not conducted or no evidence found to show it was conducted**
23240	Physical Exam Urinalysis Urine Protein/Creatinine Ratio	Weeks: 0, 2, 14, 18* Weeks: 12, 18 Screening, Weeks: 6, 12, 18
23241	Physical Exam Urinalysis Urine Protein/Creatinine Ratio	Weeks: 0, 2, 10, 14 Screening, Week 18 Screening, Weeks: 6, 18
23242	Physical Exam Urinalysis Urine Protein/Creatinine Ratio	Weeks: 2*, 6*, 10* Weeks: 18, 42 Screening, Weeks: 12, 18, 42
23243	Physical Exam Urinalysis Urine Protein/Creatinine Ratio	Weeks: 2*, 18*, 22* Week 18 Screening, 6, 12, 18
23244	Physical Exam Urinalysis Urine Protein/Creatinine Ratio	Weeks: 6*, 10, 26*, 42* Week 18, Termination Weeks: 12, 18, 24; Termination
23245	Physical Exam Urinalysis Urine Protein/Creatinine Ratio	Weeks: 0, 6*, 14*, 34* Weeks: 18, 36, 42 Screening, Weeks: 18, 36, 42
23246	Physical Exam Urinalysis Urine Protein/Creatinine Ratio	Week 30* Week 24 Screening, Weeks: 6, 18, 24; Termination
23247	Physical Exam	Weeks: 0, 6*, 30*, 38*

Subject #	Study procedure not conducted or no evidence found to show it was conducted	Study visit the procedure was not conducted or no evidence found to show it was conducted
	Urinalysis Urine Protein/Creatinine Ratio	Weeks: 18, 60 Weeks: 18, 24, 36, 60
23248	Physical Exam Urinalysis Urine Protein/Creatinine Ratio	Weeks: 0, 2, 22* Week 18 Weeks: 6, 12, 18, Termination
23249	Physical Exam Urinalysis Urine Protein/Creatinine Ratio	Weeks: 2, 6 Termination Screening, Termination
23250	Physical Exam Urinalysis Urine Protein/Creatinine Ratio	Weeks: 2, 6* Termination Termination
23251	Physical Exam Urine Protein/Creatinine Ratio	Weeks: 6*, 10*, 50* Screening

* For items noted with an asterisk above, there was no documentation found in the source records to corroborate that a protocol specified physical exam was performed as noted in the CRF.

c. Protocol Amendment #3 specified that the investigator must report all Serious Adverse Events (SAE) to the sponsor within 48 hours of observing or learning of the event. In addition, for the initial SAE, the investigator was to also record all case details that can be gathered within the 48 hours on the SAE page of the CRF. Protocol Amendment #3 further specified that investigators were required to keep the IRB informed of any significant AEs.

An office visit note dated December 7, 2005, stated that Subject # 23243 experienced grade 4 nephrotic syndrome. We note that you failed to report this SAE to the sponsor within 48 hours as required by the protocol. The report was submitted to the sponsor on an SAE form dated May 11, 2006. In addition, the SAE was not reported to the IRB until May 23, 2006.

d. Protocol Amendment #2 specified that the dose of [redacted] administered in this study was 10 mg/kg once very 2 weeks. Records indicate that on September 27, 2004, Subject #23248 received [redacted] instead of [redacted].

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Tejashri Purohit-Sheth, M.D., at 301-796-3402; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Tejashri Purohit-Sheth, M.D.
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Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
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Bldg 51, Room 5358
10903 New Hampshire Avenue
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Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

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

/s/

LESLIE K BALL
03/30/2009