DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 08-HFD-45-0501

Edward Mostel, M.D.
Palm Beach Gardens Medical Center
3370 Burns Road
Suite 205
Palm Beach, Florida 33410

Dear Dr. Mostel:

Between October 17 and October 31, 2007, Mr. Albertfiel Salvador, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of Protocol[ ]'A randomized comparison of [ ]versus[ ] in patients undergoing early invasive management for[ ]performed for[ ]

This inspection is a part of 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 the study have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your November 7, 2007 letter written in response to the Form FDA 483, 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, Investigator Salvador presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration [21 CFR 50.20]**. Specifically,

   a. Subject 01252-001[ ]signed the Informed Consent Document (ICD) on May 29, 2004, and the clinical investigator signed the same ICD on May 29, 2004. However, records document that this same subject was enrolled and administered study drug, starting on May 28, 2004 at 15:30, one day before IC was obtained.

b. Subject 01252-040[ ]signed the Informed Consent Document on December 16, 2004, and the Clinical Investigator signed the same ICD on December 16, 2004. Records document that this subject was enrolled, and administered study drug starting on December 14, 2004 at 15:30, two days before informed consent was obtained.

Your response letter dated November 7, 2007 states that these findings may have been an error in correctly dating the ICD. Your response is unacceptable, as there is no way to verify whether these subjects in fact gave written informed consent prior to administration of study drug.

2. **You failed to maintain adequate drug disposition records [21 CFR 312.62(a)].**

Specifically, the investigation found that drug accountability records were missing for nine subjects (110 through 118) between October 13, 2005 and December 5, 2005. You state in your response that "hospital records did confirm the subjects did receive study drug as per the protocol", but you provide no evidence to support your statement.

3. **You failed to conduct the study according to the investigational plan [21 CFR 312.60].** Specifically,

a. Protocol Section 15.1 requires that "once the appropriate essential information has been provided to the patient.... the patient and the investigator (or designee) shall sign the IRB or EC-approved written informed consent form." The investigation found that the ICD signed by Subject 01252-025 on October 13, 2004 was not signed or dated by the Principal Investigator or Sub-investigator.

b. The protocol excluded all subjects with prior enrollment in the study. The investigation found that Subject 01252-089[ ]was the same subject as 01252-043[ ]and was enrolled twice into this study, as confirmed by matching birthdates and social security numbers. This subject was first enrolled into the study on January 4, 2005 as Subject 043, and again on June 2, 2005, as Subject 089.

Your response letter dated November 7, 2007 acknowledges this error by your sub-investigator. Please note as the clinical investigator, you retain responsibility for oversight of the study.

4. **You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].** Specifically,

a. The protocol excluded patients with a calculated serum creatinine clearance < 30 mL/min, as determined by the Cockcroft Gault formula. The investigation found that of 50 subjects whose records were audited, source records failed to document the calculated serum creatinine clearance value for all 50 subjects.

The calculation of creatinine clearance and exclusion of subjects with creatinine clearance < 30 mL/min is crucial to ensure the safety of subjects with renal impairment. Your response letter dated November 7, 2007, states that this value was calculated, but not documented. Your explanation is unacceptable. Without documentation, there is no way to verify that subjects were eligible for enrollment into the study, as determined by calculated serum creatinine clearance.

b. The protocol required that randomization should only occur after patient eligibility is confirmed. The investigation found that the [ ] Enrollment Sheets for eight subjects failed to document if subjects met all inclusion criteria. The eight subjects were as follows: 024, 026, 033, 039, 041, 075, 098, 102.

   Your response letter dated November 7, 2007, states that each subject was considered for the trial by first reviewing all of the inclusion and all the exclusion criteria. Your explanation is unacceptable, as without documentation, there is no way to verify if these subjects were eligible for enrollment into the study.

c. You did not sign and date completed electronic Case Report Forms submitted to the sponsor for 12 subjects.

   In your response letter dated November 7, 2007, you state that the clinical investigator could authorize the sponsor to apply a signature by proxy instead direct signature. You provided a copy of a signed proxy dated January 30, 2007, which was the date that the database was locked by the sponsor, and more than 1 year after the last subject was enrolled. Your response is unacceptable, since you did not review these Case Report Forms during the course of the clinical study.

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 must 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.
Branch Chief (Acting)
Good Clinical Practice Branch 2
Division of Scientific Investigations, Bldg 51, Rm. 5358
Office of Compliance
CDER/FDA
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Leslie Ball, M.D.
Director
Division of Scientific Investigations
Bldg 51, Rm. 5342
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 Ball
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