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Inspections, Compliance, Enforcement, and Criminal Investigations

Simmons, John F, M. D. 2/18/11



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Ref: 11-HFD-45-02-02

John F. Simmons, M.D.
915 West Hospital Drive
Geneva, AL 36340-1645

Dear Dr. Simmons:

Between July 26 and August 10, 2010, Ms. Patricia Smith, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations of the investigational drug **(b)(4)**, performed for **(b)(4)**:

- Protocol **(b)(4)** entitled **(b)(4)** and **(b)(4)**
- Protocol **(b)(4)** entitled **(b)(4)**

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

From our review of the establishment inspection report, the documents submitted with that report, and your written response dated August 31, 2010, 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, Ms. Smith presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].

When you signed the Statement of Investigator (Form FDA 1572) for the above-referenced clinical trials, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trial is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60]. By signing the Form FDA 1572, you specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator, you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and that these trials were conducted in a manner that protects the rights, safety, and welfare of human

subjects.

We note that your failure to adequately supervise this study led to significant problems with the conduct of the study as described below, including the enrollment of subjects who did not meet eligibility criteria and the failure to perform study-required procedures related both to subject safety and to the efficacy endpoints within the protocol time frames.

2. You failed to conduct the studies or ensure that they were conducted according to the signed investigator statement and the investigational plan, and to protect the rights, safety, and welfare of the subjects under your care [21 CFR 312.60].

As the clinical investigator, you are responsible for ensuring that the investigation was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and for protecting the rights, safety, and welfare of study subjects. Specifically:

- a. Protocol **(b)(4)**, Section 4.2.2, Exclusion Criteria, Subsection 1, excludes subjects at screening with conditions that contraindicate the use of **(b)(4)** therapy with **(b)(4)**. Subject #140360013 was enrolled in protocol **(b)(4)** with a known allergy to **(b)(4)**, which was documented in the subject's medical history.
- b. Protocol **(b)(4)**, Section 4.2.2, Exclusion Criteria, Subsection 4, excludes subjects at screening with severe renal insufficiency, which is defined in the protocol as a calculated creatinine clearance (CrCl) less than 30 mL/min.
 - i. Creatinine clearance screening, which is designed to measure kidney function, was not performed at the screening visit for 22 of the 31 subjects enrolled in the study. As you should be aware from the protocol, the investigational drug **(b)(4)** is excreted, in part, through the kidneys,
 - ii. Subjects #140360015 and 140360016 were enrolled into the study with screening CrCl values of 29 and 21 mL/min, respectively.
- c. Protocol **(b)(4)**, Section 4.2.2, Exclusion Criteria, Subsection 2, excludes subjects at screening with an **(b)(4)** greater than 1.5.
 - i. An **(b)(4)**, which is designed to evaluate **(b)(4)**, was not obtained at the screening visit for 23 of the 31 subjects enrolled in the study.
 - ii. Subject #140360019 was enrolled into the study with a screening **(b)(4)** of 1.9.
- d. Protocol **(b)(4)**, Section 4.5.7, Prior and Concomitant Therapy, permitted the concomitant use of **(b)(4)** in total daily doses not to exceed 100 mg when administered once daily in subjects with **(b)(4)** disease. Subjects #140360005, 140360013, and 140360016 were enrolled into the study with a 325 mg/day use of **(b)(4)** documented in their medical histories. Subjects #140360005 and 140360013 have **(b)(4)** disease documented in their medical histories, and the screening records for Subject #140360016 indicated that the subject did not require more than a 2-day prophylactic use of an **(b)(4)**.

With respect to the findings noted above, 5 of the 31 subjects you enrolled into the study should have been excluded during the screening process. In addition, it is unclear whether 23 additional subjects randomized were eligible for enrollment into the study, because you did not conduct the protocol-required creatinine clearance screening and/or did not obtain **(b)(4)** at screening for these subjects. Therefore, you jeopardized the safety and welfare of 5 subjects by enrolling them into a study for which they were ineligible, and another 23 subjects by not conducting required creatinine clearance screening and/or by not obtaining required screening **(b)(4)**.
- e. Protocol **(b)(4)** stipulates that an ultrasonography to determine efficacy should be performed after the last parenteral dose of study medication, within 24 hours of its administration on visit Day 10.

Of the 31 subjects enrolled in the study, 10 subjects received the ultrasonography more than 24 hours after the last parenteral dose, and 3 subjects received the ultrasonography prior to receiving the last parenteral dose.

Enrollment of subjects who do not meet eligibility criteria and failure to perform study-related procedures jeopardize subject safety and welfare and compromise the interpretation and validity of the investigational endpoints.

In your response dated August 31, 2010, you acknowledge that a number of procedures were not appropriately followed. You alleged that you misinterpreted the protocol procedures and that you were

not given any guidance or clarification from the sponsor until well into the study. In addition, your response concludes with the statement that you have initiated corrective action and retraining of staff. We acknowledge your response. However, we are concerned that the response is not adequate to prevent future recurrence of the violation noted above, because you failed to provide the details of your corrective actions and the staff retraining.

3. You failed to report promptly to the IRB all changes in the research activity [21 CFR 312.66].

FDA regulations require that the clinical investigator shall assure that they will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that they will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects [21 CFR 312.66].

You failed to notify the IRBs of the following changes in the research activities:

- a. You failed to inform the IRB that on May 4, 2009, the sponsor of Protocol **(b)(4)** placed your site on temporary recruitment hold, based on your site's systematic deviations and the inability of the study monitors to gain access to all subjects' medical histories.
- b. You failed to inform the IRB that on August 18, 2009, the sponsor of Protocol **(b)(4)** notified you of their closure of your site due to significant noncompliance with good clinical practices.
- c. You failed to notify the IRB until July 16, 2009, that enrollment of Protocol **(b)(4)** had been halted by the sponsor on May 7, 2009.

In your response dated August 31, 2010, you state that the sponsor of Protocol **(b)(4)** notified the IRB of the temporary recruitment hold and the termination of your participation in the study and the site closure. This response is unacceptable, because you did not address your responsibility as a clinical investigator to promptly report to the IRB all changes in research activity. Moreover, you failed to address your delay in notifying the IRB of Protocol **(b)(4)** enrollment halt at your site.

In your response, you state that all of the observed issues were corrected immediately once they were identified and brought to your attention. Your response is inadequate, because you failed to provide the details of the corrective action that would prevent such occurrences in the future.

Failure to promptly report changes in the research activity to the IRB compromises the safety and welfare of subjects enrolled in the clinical investigation.

4. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60].

Except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative [21 CFR 50.20].

As an investigator, it is your responsibility to obtain informed consent in accordance with 21 CFR part 50. Except as provided in 21 CFR 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form [21 CFR 50.27(a)].

You failed to obtain legally effective informed consent from Subject #1403060015, who was prescribed the investigational new drug, **(b)(4)**. Specifically, the informed consent form for Subject #1403060015 in Protocol **(b)(4)** was signed by someone other than the subject. During the inspection, it was observed that both the handwriting and the signature of Subject #1403060015 were inconsistent between the subject's consent documents and the subject's study diary.

In your response dated August 31, 2010, you acknowledge that someone other than the subject signed the consent documents because the subject's hands were shaking. However, you failed to confirm or document that this person was the subject's legally authorized representative. The regulations require that informed consent be signed and dated by the subject or the subject's legal representative prior to the subject's involvement in the investigation [21 CFR 50.20]. Failure to obtain adequate informed consent jeopardizes the safety and welfare of enrolled subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

We acknowledge your response. However, we are concerned that the response is inadequate, since you did not propose corrective actions to prevent future recurrence of the violation noted above.

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 ongoing 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 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 Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity (formerly Lewin), M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

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
Food and Drug Administration

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
02/18/2011

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