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Inspections, Compliance, Enforcement, and Criminal Investigations

Griffin, John M.D. 3/14/11



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-45-02-01

John Griffin, M.D.
Cardiovascular Associates, Ltd.
1708 Old Donation Parkway
Virginia Beach, VA 23454

Dear Dr. Griffin:

Between May 12 and July 15, 2010, Ms. Sherry Secrist, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations:

- Protocol **(b)(4)**, entitled "**(b)(4)**" of the investigational drug **(b)(4)**, performed for **(b)(4)**; and
- Protocol **(b)(4)**, entitled "**(b)(4)**" of the investigational drug **(b)(4)**, performed for **(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 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, Ms. Secrist presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your August 13, 2010, response to Form FDA-483, but note that this response was received past the 15 working days from close of the inspection. Thus, while we have reviewed the response, we have not included a discussion of the response in this letter, as per the Commissioner's Enforcement Initiative announced August 11, 2009.

We wish to emphasize the following:

- 1. You failed to ensure that the investigation was conducted according to the signed**

investigator statement, in that 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 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.

Specifically, you failed to adequately supervise the research nurse to whom you delegated tasks. Your failure to adequately supervise the research nurse caused many of the other violations listed in this letter. For example, your research nurse improperly completed or signed your name on documents related to Protocol **(b)(4)**, such as the Form FDA 1572 dated October 11, 2007, a nondisclosure agreement dated July 12, 2007, and the confidential study protocol dated August 8, 2007; and documents related to Protocol **(b)(4)** that include an IRB financial disclosure form dated January 14, 2008, two serious adverse event reports to the IRB dated January 25, 2008, and the signature and delegation form. Additionally, as noted in Item 2 below, two of four subjects randomized in Protocol **(b)(4)** did not meet eligibility criteria as required by the protocol. Had you provided adequate oversight, you would have observed from a review of the study documents that the signatures on the study-related documents were not yours and that the two randomized subjects were not eligible according to the protocol.

We note, according to your multiple letters to the various stakeholders [**(b)(4)**, Sentara Virginia Beach General Hospital (SVBGH) IRB, **(b)(4)** (sponsor of Protocol **(b)(4)**), **(b)(4)**(sponsor of Protocol **(b)(4)**), and **(b)(4)**] dated February 22, March 5, March 9, March 14, March 17, March 19, March 26, April 3, May 19, June 2, and June 5, 2008, that you were first made aware of the situation regarding improper signatures by one of your research nurses on February 20, 2008. You reported that you conducted an internal investigation on February 21, 2008, in which the research nurse reportedly admitted to your office manager that she had improperly signed your name to documents. This internal investigation reportedly resulted in termination of employment of the responsible research nurse, as well as notification of her actions to the State Board of Nursing. You notified the IRB on February 22, 2008, of the situation involving your research nurse and the inappropriate signatures, and you immediately voluntarily placed your active studies on hold to screening and enrollment.

Additionally, we note, according to your multiple letters to the various stakeholders, that you reported that an internal audit was conducted on February 27 and 28, 2008, and that you received preliminary audit results on March 3, 2008. You indicated that a corrective action plan was implemented on March 5, 2008, that included repeating the informed consented process of the enrolled subjects; evaluation and updating of source documentation; modification of your research Standard Operating Procedures; and resubmission of affected documents. We note that as a result of the sponsor's finding of serious noncompliance with respect to Good Clinical Practice (GCP), the sponsor for Protocol **(b)(4)** terminated your site. In addition, due to the GCP noncompliance, the SVBGH IRB suspended approval indefinitely and halted enrollment for all other studies in which you participated until the IRB could independently confirm the extent of involvement of the research nurse and verify the level of misconduct.

In your June 2, 2008, written correspondence to **(b)(4)**, you stated that "...we accept that the Memos to File we wrote indicate the lack of knowledge or approval of four patients enrolled" We note that your failure to adequately supervise these studies led to significant problems with the conduct of the studies, including the submission of improper signatures on study-related documents to both the IRB and the sponsor, as well as the randomization of ineligible subjects in Protocol **(b)(4)**, as described in Item 2 below.

We acknowledge that you identified the problem and have established certain corrective actions. We also acknowledge that through your corrective actions, you identified and addressed the integrity of the investigational procedures and data in the other clinical investigations in which the terminated research nurse was involved. However, we find that you have not adequately addressed how you will improve your supervision of study staff in the future.

2. You failed to conduct the studies or ensure they were conducted according to the investigational plan [21 CFR 312.60].

a. You failed to ensure that the research nurse to whom you delegated the responsibility of reviewing the eligibility criteria understood the inclusion criteria for Protocol **(b)(4)**. Inclusion criterion #2 states:

Subject must have evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems as follows:

a. CAD as indicated by a history of presumed spontaneous MI (hospitalized with final diagnosis of MI, excluding periprocedural or definite secondary MI [eg, due to profound anemia or hypertensive emergency, troponin increase in sepsis]) ≥ 2 weeks but ≤ 12 months prior

b. ischemic (presumed thrombotic) CVD as indicated by a history of ischemic stroke (hospitalized with final diagnosis of non hemorrhagic stroke) ≥ 2 weeks but ≤ 12 months prior

c. PAD as indicated by a history of intermittent claudication and

- i. an ankle/brachial index (ABI) of < 0.85 , or
- ii. amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia

We note that Subjects 00272 and 00276 were enrolled in the clinical investigation even though they did not satisfy the inclusion criterion noted above. We note that you placed a "Memo to File" dated March 11, 2008, in both subjects' study records that stated, in part, "...randomized to study without my review and approval of the screening data. I reviewed all screening data. The subject did not meet inclusion criteria for the trial."

b. Section 5.7.1 of Protocol **(b)(4)** requires that CK and CK-MB "...blood samples be taken 2 hours (+ 1 hour) after the index procedure, and then every 8 hours (+/- 1 hour) for the next 24 hours or until hospital discharge ...". You failed to ensure that Subject 301082002 had the required timing of and number of post-procedural blood samples obtained prior to discharge.

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

We acknowledge that you have established corrective actions to ensure that subject screening data collection and review for eligibility prior to enrollment, and the completion of protocol-required assessments, will occur in the future.

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 believe that your August 13,

2010, written response to the Form FDA 483 fully explains the actions you have taken to prevent similar violations in the future, please communicate that to us in writing within fifteen (15) business days. You may reference the written response dated August 13, 2010, in your response to this letter.

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
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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

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/s/

LESLIE K BALL
03/14/2011

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