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Inspections, Compliance, Enforcement, and Criminal Investigations

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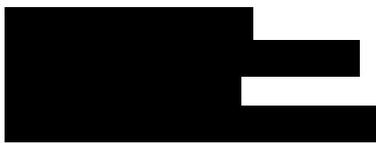


Department of Health and Human Services

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

WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**



Dear Dr. [REDACTED]

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between October 12 and December 5, 2012. Ms. Yvette LaCour-Davis, representing the FDA, reviewed your conduct of the following clinical investigations of the investigational drug (b)(4) ((b)(4)), performed for (b)(4)

- Protocol (b)(4), "(b)(4)"; and
- Protocol (b)(4), "(b)(4)."

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

At the conclusion of the inspection, Ms. LaCour-Davis presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your December 24, 2012, written response to the Form FDA 483.

From our review of the FDA establishment inspection report, the documents submitted with that report, and your December 24, 2012, written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol **(b)(4)** required you to exclude subjects who met the exclusion criteria and who did not meet the inclusion criteria. You failed to adhere to this requirement. Specifically:

The investigational plan for Protocol **(b)(4)** required all subjects to be at "high cardiovascular risk." To meet this requirement, subjects must have at least one of the following high-risk conditions prior to screening and enrollment:

- History of myocardial infarction (>2 months prior to informed consent);
- Unstable angina (>2 months prior to informed consent) with documented multivessel coronary disease (of at least two major coronary arteries in angiogram) or positive stress test (ST segment depression ≥ 2 mm or a positive nuclear perfusion scintigram);
- Multivessel Percutaneous Coronary Intervention (PCI) > 2 months prior to informed consent;
- Multivessel Coronary Artery By-pass Grafting (CABG) > 4 years prior to informed consent or with recurrent angina following surgery;
- History of ischemic or hemorrhagic stroke (> 2 months prior to informed consent); or
- Peripheral occlusive arterial disease (previous limb bypass surgery or percutaneous transluminal angioplasty; previous limb or foot amputation due to circulatory insufficiency; angiographic or imaging detected (for example: ultrasound, MRI) significant vessel stenosis (> 50% stenosis) of major limb arteries).

We note that this list does not include transient ischemic attack (TIA), deep venous thrombosis, or peripheral arterial disease without previous surgery or significant vessel stenosis (greater than 50%) detected by angiography or imaging, which were the cardiac-related conditions documented for the subjects described below.

Five of eleven subjects at your site were randomized into Protocol **(b)(4)** without having met the protocol requirement for being at high cardiovascular risk.

a. Subject 56782: At the December 10, 2010, screening visit, the only cardiovascular condition documented was transient ischemic attack. This subject was not excluded from enrollment and treatment randomization.

b. Subject 56784: At the December 14, 2010, screening visit, the only cardiovascular conditions documented were transient ischemic attack and transient peripheral arterial disease of the left limb without past surgery or confirmation of significant vessel stenosis detected by angiography or imaging. This subject was not excluded from treatment randomization.

c. Subject 56791: At the January 5, 2011, screening visit, the only documented cardiovascular condition was transient ischemic attack. This subject was not excluded from treatment randomization.^[1]

d. Subject 56799: On the screening narrative, dated January 5, 2011^[2], the only cardiovascular condition documented was transient ischemic attack. This subject was not excluded from treatment randomization.

e. Subject 56795: At the January 6, 2011, screening visit, the only cardiovascular condition documented was deep venous thrombosis of the leg. This subject was not excluded from treatment randomization.

In your December 24, 2012, written response to the violations noted in Items 1.a through 1.e. above, you acknowledged that the subjects described were enrolled into Protocol **(b)(4)** without meeting protocol-specified criteria for being at high cardiovascular risk. Your response is inadequate because you have not provided sufficient information to enable FDA to evaluate the adequacy of your corrective action

plan. Although you stated in your written response that you will follow protocol inclusion/exclusion eligibility criteria, you did not provide any details describing how you plan to prevent recurrence of similar violations in the future.

Enrollment of subjects who do not meet eligibility criteria jeopardizes subject safety and welfare, and raises concern about the validity and integrity of the data collected at your site.

2. You failed to obtain Institutional Review Board (IRB) approval for changes in the research prior to implementing the changes [21 CFR 312.66].

As a clinical investigator, you are required to obtain IRB approval for any changes in the research, except where necessary to eliminate apparent immediate hazards to human subjects. You failed to obtain IRB approval for changes in the research that were not related to the elimination of apparent immediate hazard to subjects. Specifically:

Your site implemented changes contained in Protocol **(b)(4)**, Revision 3 (Version 4), dated December 29, 2011, before you received IRB approval for this version of the protocol. Protocol **(b)(4)**, Version 4 contains multiple changes, including significant changes to the inclusion criteria. These changes include revisions to Section 3.3.2 of the inclusion criteria that redefine patients' cardiovascular eligibility risk factors to include patients with single-vessel disease and peripheral artery disease who have not undergone any corrective surgical intervention. These revisions are a significant expansion of the inclusion criteria from those in Version 1 of Protocol **(b)(4)**. There is no documentation to show that the amendments to Protocol **(b)(4)**, Version 4 were ever approved by the IRB. This newer version of Protocol **(b)(4)** should not be used unless IRB approval has been received. Without documentation of IRB approval for these revisions (which do not qualify for an exception from IRB approval, as they are unrelated to the elimination of apparent immediate hazards to human subjects) in Version 4 of Protocol **(b)(4)** prior to implementation, you have failed to meet the requirements of 21 C.F.R. § 312.66.

In your December 24, 2012, written response to the violation noted in Item 2 above, you said, "The monitor failed to inform and educate the site about the amendment to the Protocol #**(b)(4)**, revision 03, dated 29 Dec 2011 was approved [*sic*] by the IRB." We interpret this to mean that the study monitor failed to inform the staff of IRB approval of a new version of Protocol **(b)(4)**. However, it is your responsibility as the investigator (not the monitor's responsibility) to ensure that the IRB has approved any changes in the research prior to implementing those changes. In addition, your response is inadequate because you failed to provide evidence of IRB approval or a corrective action plan to prevent recurrence of similar violations in the future.

Your failure to obtain IRB approval for research changes prior to implementing those changes prevented the IRB from making an informed determination regarding the continued safety of the subjects enrolled in your investigational research.

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 address the violations noted above adequately and promptly 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, M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations