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Inspections, Compliance, Enforcement, and Criminal Investigations

Michelson, Joseph B., M.D. 7/6/11



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-45-06-01

Joseph B. Michelson, M.D.
11423 187th St., Suite 200
Artesia, CA 90701

Dear Dr. Michelson:

Between July 26 and August 24, 2010, Thomas R. Beilke, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol **(b)(4)**, entitled **(b)(4)**) performed for the **(b)(4)**. We note that you became the clinical investigator responsible for the study on March 2, 2009, and that, prior to that time, Laura A. Teasley, M.D., was the clinical investigator responsible for the study.

This inspection is a part of the 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 and your written response dated September 8, 2010, 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. Beilke presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

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

a. Chapter 2, Section 2.2.2 of the protocol (Version 5.0, dated March 24, 2008) specified an inclusion criterion of diabetic macular edema present on clinical exam and central subfield thickness on optical coherence tomography (OCT) \geq 250 microns, within 8 days of randomization. OCT scans were taken off-center for the subjects identified below. Thus, readings taken made subjects appear eligible when they may not have been.

- i) Subject 0046 **(b)(6)**'s OD eye dated May 20, 2009
- ii) Subject 0042 **(b)(6)**'s OS eye dated April 22, 2009

We acknowledge the corrective actions described in your September 8, 2010, written response to Form FDA 483 that you will be taking to prevent inclusion of subjects with off-centered OCT scans in the future. However, regardless of your corrective actions, as the clinical investigator, you were ultimately responsible for the conduct of this study and for ensuring that all subjects enrolled in the study were eligible.

b. Chapter 3, Section 3.2 of the protocol (Version 5.0, dated March 24, 2008) specified that all study eyes were to receive **(b)(4)** with **(b)(4)**. Six of 18 eyes enrolled in the study did not receive **(b)(4)**.

Specifically:

- i) Subject 0044 **(b)(6)** received **(b)(4)** on May 7, 2009 and **(b)(4)** on May 14, 2009 for a total of **(b)(4)** to the OS eye.
- ii) Subject 0045 **(b)(6)** received **(b)(4)** on May 19, 2009 and **(b)(4)** on June 2, 2009 for a total of **(b)(4)** to the OD eye.
- iii) Subject 0045 **(b)(6)** received **(b)(4)** on May 20, 2009 and **(b)(4)** on June 3, 2009 for a total of **(b)(4)** total **(b)(4)** to the OD eye.
- iv) Subject 0043 **(b)(6)** received **(b)(4)** on May 14, 2009 and **(b)(4)** on May 20, 2009 for a total of **(b)(4)** to the OD eye.
- v) Subject 0041 **(b)(6)** received **(b)(4)** on February 26, 2009 and **(b)(4)** on April 2, 2009 for a total of **(b)(4)** to the OS eye.
- vi) Subject 0046 **(b)(6)** received **(b)(4)** on May 27, 2009 and **(b)(4)** on June 3, 2009 for a total of **(b)(4)** to the OD eye.

We acknowledge your statement in your September 8, 2010, written response that, although at the initial evaluation, you felt that at least **(b)(4)** additional **(b)(4)** would be possible, at the time of treatment, it was not possible to place the additional **(b)(4)** as required by protocol. The protocol required a certain number of **(b)(4)** and did not allow flexibility. However, your written response did not explain nor did you provide any evidence that you removed these subjects from the study after realizing that they were unable to receive the required number of **(b)(4)**. Keeping these subjects in the study compromised data integrity.

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 Enforcement Branch
Division of Good Clinical Practice Compliance
Office 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.
Acting Office Director
Office 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
07/06/2011
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