Keith A. Aqua, M.D. 9/2/14

Dear Dr. Aqua:

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 February 3 and March 17, 2014. Ms. Colleen Aspinwall, representing 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)”;
- 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. Aspinwall presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your March 24, 2014, written response to the Form FDA 483.
From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your written response dated March 24, 2014, 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 Protocols (b)(4) and (b)(4) required that subjects self-record all pain assessments and have certain laboratory assessments completed. You failed to adhere to these requirements. Specifically:

   a. Protocols (b)(4) and (b)(4) required that during the study period, subjects self-record all scores for pain-intensity and pain-relief assessments. However, site staff, rather than the subjects, recorded pain-intensity scores for the 20 subjects enrolled in Protocol (b)(4) and for the 3 subjects enrolled in Protocol (b)(4). Of note, the primary efficacy endpoint for both studies was based on the pain-intensity scores that the subjects self-recorded.

   In your March 24, 2014, written response, you stated, “The pain intensity scores were recorded by the study staff in the diary.” You indicated that the contract research organization (CRO) instructed site staff to “ask the patient the pain scores and then to record them in the diary for the patient.” In addition, you indicated that in the immediate postoperative setting, you felt it was impossible for subjects to self-record assessments into a workbook.

   We acknowledge the corrective actions that you have taken regarding the findings noted in Item 1.a. above. You indicated in your written response that, along with other corrective actions, you have instituted strict adherence to the protocol, and that you will seek justification and written documentation for any protocol deviation.

   Your response is inadequate because it does not contain sufficient detail. Specifically, you did not provide details regarding how you will implement your corrective action plan. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations in the future.

   b. Protocols (b)(4) and (b)(4) required that you obtain subjects’ local laboratory results for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin, creatinine, and blood urea nitrogen, both at screening and at study termination (or within 24 hours after termination). These laboratory values were to be used to identify subjects with surgically induced renal or hepatic impairment, whether pre-existing or acute.

   i. For 8 of the 13 subjects whose records were reviewed for Protocol (b)(4), you failed to obtain some or all of the laboratory results that were required at the end of
the study. Specifically, for Subjects 15-907, 15-911, 15-912, and 15-917, you did not obtain results for ALT, AST, and total bilirubin; and for Subjects 15-901, 15-902, 15-903, and 15-904, you did not obtain any of these required laboratory results.

ii. For 2 of the 3 subjects enrolled in Protocol (b)(4) (Subjects 53-903 and 53-904), you failed to obtain results for AST, ALT, and bilirubin, either at screening or at the end of the study.

In your March 24, 2014, written response to the findings noted in Item 1.b. above, you indicated that many times, end-of-study laboratory tests were not performed even when ordered, and that protocol compliance was difficult to maintain.

We acknowledge the corrective actions that you plan to take in the future regarding the findings noted in Item 1.b. above. You indicated in your written response that, along with other corrective actions, you will take every measure to ensure that study obligations will be met; that all labs will be drawn throughout trials in accordance with the protocols; and that you personally will review all study laboratory results and ensure that these are obtained and documented in a timely fashion.

Your response is inadequate because it does not contain sufficient detail. Specifically, you did not provide details regarding how you will implement your corrective action plan. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations 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 address the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

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
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
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Sincerely yours,

{See appended electronic signature page}
Sean Y. Kassim, Ph.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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/s/

DAVID C BURROW on behalf of SEAN Y KASSIM
09/02/2014

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