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Inspections, Compliance, Enforcement, and Criminal Investigations

Scott, David F., M.D.



Department of Health and Human Services

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

WARNING LETTER

Oct 20, 2010

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Ref: 11-HFD-45-10-06

David F. Scott, M.D.
785 E Holland Avenue
Spokane, WA 99218-1257

Dear Dr. Scott:

Between March 15 and March 24, 2010, Dr. S. Lori Brown and Dr. Sunitha Rajaram, 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)**, "**(b)(4)**" of the investigational drug **(b)(4)**, performed for **(b)(4)**.
- Protocol **(b)(4)**, "**(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, the documents submitted with that report, and your written response dated April 6, 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, Drs. Brown and Rajaram presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to ensure that the investigations were conducted according to the signed investigator statements and the investigational plans [21 CFR 312.60].

a. Protocol **(b)(4)**:

- i. The protocol states, "Once the subject meets all of the inclusion criteria and none of the exclusion criteria, and the knee replacement surgery has been completed, the investigator or the investigator's designee will contact the IVRS to randomize the subject into the study." Ten subjects (Subjects 002, 003, 004, 005, 006, 008, 009, 010, 011, and 013) were randomized into the study before surgery, contrary to the protocol, prior to sponsor's approval of your request for exemption, dated May 7, 2008.
- ii. The protocol required a complete physical examination for each randomized subject at Day 10 (completion of study) or upon early termination, prior to venography, for the day that the venogram was to be performed (Day 10, Visit 7). You failed to perform this physical examination for any of the randomized subjects in this study.

iii. The protocol states, for visit 5: "Collect blood samples for Pharmacokinetic testing for subjects randomized to (b)(4) only. The samples should be collected at pre-dose, 2, 6, and 12 hours post-dose." Pharmacokinetic (PK) data was a secondary endpoint of the (b)(4) study.

PK testing was not performed on 11 of the 13 subjects for whom it was required (002, 003, 004, 006, 010, 011, 013, 014, 015, 016, and 017). The (b)(4) laboratories document indicates that the sample was not received, and the eCRF indicates that PK collection was not performed.

iv. Eligibility criteria are designed specifically for each clinical investigation by the sponsor to optimize the interpretability of the data to the disease process under study and to minimize foreseeable harm to enrolled subjects due to comorbidities and possible interactions with concomitant medications.

Protocol exclusion criterion # 16 states, "The subject is taking aspirin > 162 mg/day."

Source documents indicate that subject 4033017 was taking aspirin while participating in the study.

- Bufferin brand aspirin, with a dose of 325 mg, is listed in the case report form (CRF) under Concomitant Medication, with a start date of 2006 and an end date of (b)(4).
- In addition, Bufferin is included in the source documents (b)(4): Medical History dated (b)(4), under Current Medications).
- Documentation is also found in (b)(4), Medication Reconciliation, Admission Medication Orders: Aspirin (Bayer) 1-2 By Mouth As Needed (date: (b)(4)); and (b)(4), Medication Reconciliation, Admission Medication Orders: Aspirin (Bayer) 1-2 By Mouth As Needed, Last Taken: (b)(4).

v. The protocol indicates that a bilateral venography procedure was required at the End of Treatment or at Early Termination. Venography was not performed for 7 of 16 randomized subjects. For example:

Subjects 017, 018, and 019 did not have venography at the End of Treatment/Day 10 (Visit 7) due to scheduling conflicts and/or technical problems at the radiology clinic.

vi. The sponsor sent you a letter dated June 16, 2008, instructing you to suspend screening new subjects into the study. However, you screened Subject 4033021 into the study on July 23, 2008.

b. Protocol (b)(4):

i. The protocol requires a physical examination at Visit 6 (end of treatment) on the day of the venography procedure.

Subject 72001 had Visit 6 (end of treatment) on August 19, 2008. A physical examination was not conducted at this visit.

ii. The protocol requires a blood sample to be sent to the central laboratory for Liver Function Test (LFT) monitoring at Visit 5 or Day of Discharge. A blood sample for LFT was not drawn and sent to the central laboratory for Subject 72001 on July 25, 2008 (Visit 5) due to hospital error. Instead, these laboratory tests were performed in a local laboratory on August 08, 2008.

iii. The protocol requires a blood sample for laboratory evaluations at Visit 1/Screening Visit. Subject 72004 had Visit 1 on July 18, 2008, but blood samples were not collected until August 22, 2008.

Failure to perform study-related procedures jeopardizes subject safety and welfare, and compromises the interpretation and validity of the investigational endpoints.

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

Protocol (b)(4) required randomization of subjects after completion of the surgery. All of the subjects were randomized prior to surgery. After the randomization of 10 of the 16 subjects, sponsor approved your request for an exemption from this protocol requirement (dated May 7, 2008). You failed to obtain the IRB approval for this change.

Making changes in the research without IRB approval compromises the safety and welfare subjects enrolled in the clinical investigation.

3. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

a. For Protocol (b)(4), the Integrated Voice Response System (IVRS) site's user manual states: "Complete call worksheets prior to contacting the IVRS; then file completed worksheets with each subject's source documentation." The IVRS worksheets were not kept in the subjects' files or maintained at the site.

b. For Protocol **(b)(4)**, subject eligibility forms in the source document were not filled out. The protocol states in Section 6.2.1, Visit 1: Screening period (Days -14 to Day -1), "Pre-Screen patient for eligibility by checking inclusion/exclusion criteria." For example, source documents for Subjects 72003 and 72008 show that all the items in the exclusion criteria checklist are checked except for the exclusion criterion related to the history of thrombocytopenia, including heparin-induced thrombocytopenia, or a platelet count < 100,000 cells/micro liter. However, the eCRFs show that all the exclusion/inclusion criteria are checked.

Failing to maintain adequate and accurate case histories compromises the interpretation and validity of the investigational endpoints.

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:

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Good Clinical Practice Branch I
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Sincerely yours,
{See appended electronic signature page}
Leslie K. Ball, M.D.
Director
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/s/

LESLIE K BALL
10/20/2010

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