DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Daniel S. Berger, M.D.
Northstar Medical Center
2835 N. Sheffield Avenue, Suite 500
Chicago, IL 60657

Dear Dr. Berger:

Between March 11 and April 3, 2009, Ms. Susan Yuscius, representing the 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) of the investigational drug (b) (4) performed for (b) (4)

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

At the conclusion of the inspection, Ms.Yuscius presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We have reviewed the inspection report, the documents submitted with that report, and your written response to Form FDA 483 dated April 6, 2009. We do not find your response to be acceptable in addressing the matters under complaint, which are described below.

Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately submitted false information to the sponsor or FDA in required reports and repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products as published under Title 21, Code of Federal Regulations (CFR), part 312.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR 312.70.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You repeatedly or deliberately submitted false information to the sponsor in a required report [21 CFR 312.70(a)].**

   Multiple documents contain falsified information. For example:

   a. For Subject 010414, the following forms contained fraudulent signatures, which represented that the forms were signed by one of the sub-investigators: Northstar Healthcare form dated 7/29/08, Inclusion Criteria form dated 7/29/08, Exclusion Criteria form dated 7/29/08, Assessment of (b) (4) Illnesses/Events form dated 7/29/08, Medical/Surgical History form dated 7/29/08, Physical Examination form dated 7/29/08, and the report for the EKG performed on 7/29/08.

   b. For Subject 010420, the following forms contained fraudulent signatures, which represented that the forms were signed by one of the sub-investigators: Northstar Healthcare form dated 9/2/08, Inclusion Criteria form dated 9/2/08, and Exclusion Criteria form dated 9/2/08.

   c. For Subject 010411, the (b) (4) and (b) (4) History form dated 7/9/08 contained a fraudulent signature, which represented that the form was signed by one of the sub-investigators.

   d. For Subject 010412, the report for the EKG performed on 8/25/08 contained a fraudulent signature, which represented that the form was signed by one of the sub-investigators.

   e. For Subject 010410, the following forms contained fraudulent signatures, which represented that the forms were signed by one of the sub-investigators: Northstar Healthcare form dated 7/9/08, Assessment of (b) (4) Illnesses/Events form dated 7/9/08, and Laboratory Results signed on 7/18/08. In addition, the signature and printed name appearing on page 12 of the Patient Information and Informed Consent Documentation (PIICD) dated 7/9/08 do not resemble the signature and printed name found in other medical records containing the subject's signature and printed name. The last name of the subject is also spelled differently on the PIICD than it is on other medical records for this subject.

   f. For Subject 010417, the PIICD dated 7/30/08, and the Patient Stipend Signature Sheet dated 7/30/08, 8/11/08, 8/27/08, 9/18/08 and 9/30/08 contained fraudulent signatures, which represented that the forms were signed by the subject. The person identified as Subject 010417 did not participate in the study and the signatures on the PIICD and Patient Stipend Signature Sheet were forgeries.

g. For Subject 010419, the signature and initials on the PIICD dated 7/30/08 do not resemble those appearing on an informed consent document signed in 2006 by the person identified as Subject 010419. Although it was permissible for a legally authorized representative to sign the PIICD in the place of the subject, if the PIICD was signed by a legally authorized representative, the relationship of that person to the subject was required to be included on page 12 of the PIICD. For Subject 010419, however, the line for providing the legally authorized representative's relationship to the subject is blank, and thus there is no indication on the PIICD that his legally authorized representative signed in his place. Therefore, it appears that Subject 010419's signature was a forgery. The subject's first name is also spelled two different ways on the PIICD dated 7/30/08.

We acknowledge that in your April 6, 2009 response to Form FDA 483 you stated that the study coordinator "fictitiously created" the Laboratory Results, EKG, and Physical Exam documents listed above. Further, you stated that the study coordinator "fraudulently signed investigators' and patients' names during the consenting, screening, and follow-up process."

Review of the submitted inspectional exhibits suggests that the study coordinator began falsifying documents in July 2008. We acknowledge your position that the study coordinator falsified documents without your knowledge and also acknowledge that we do not have evidence to suggest that you were aware of the falsification before September 2008. We further acknowledge that according to a November 10, 2008, memorandum from the study coordinator and your memorandum to (b)(4) dated January 12, 2009, 1) you were first notified of informed consent irregularities at the site in September 2008 and at that time investigated the issue; 2) you confronted the study coordinator, who admitted to falsifying two informed consent documents; 3) you gave the study coordinator a written reprimand, one week leave without pay, and assigned a supervisor to monitor his study activities; and 4) you immediately terminated the study coordinator after the November 2008 sponsor audit revealed further evidence of falsification. When you were first notified of the study coordinator's actions in September 2008, however, you failed to investigate for additional acts of falsification within the same clinical investigation or in other clinical investigations in which the study coordinator was involved.

We also acknowledge the corrective actions described in your April 6, 2009, written response that you have taken to prevent the submission of false information to a sponsor in the future. However, these corrective procedures do not specify how you will address the protection of the study subjects and the integrity of investigational data in the other clinical investigations in which the study coordinator was involved (as indicated in the list of other studies Northstar Medical Center provided to FDA during the investigation). Moreover, regardless of your corrective actions, as the principle investigator you were ultimately responsible for the conduct of this study, including the fact that false information was submitted to the sponsor.

2. 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 trial, 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 in a manner that protects the rights, safety, and welfare of human subjects.

Specifically, you failed to adequately supervise the study coordinator to whom you delegated tasks. Your failure to adequately supervise the study coordinator caused many, if not all, of the other violations listed in this letter. For example, as described in item 3 below, six subjects did not receive EKG screenings at visit 0 as required by the protocol. Had you provided adequate oversight, it would have been obvious from a review of the study documents that required EKG screenings were not being performed. Similarly, in your April 6, 2009, written response to Form FDA 483 you admitted that had you reviewed the "patient roster," you would have noticed irregularities and been able to stop the study coordinator's violations.

We note that in your response to Form FDA 483 you agreed that the study coordinator did not conduct the study according to the investigational plan, and you stated that you were not aware of his activities. We acknowledge that you have established corrective actions to improve your supervision in the future. However, these corrective procedures do not specify how you will address the integrity of the investigational procedures and data in the other clinical investigations in which the study coordinator was involved (as indicated in the list of other studies Northstar Medical Center provided to FDA during the investigation). Moreover, regardless of your corrective actions, your failure to supervise your study coordinator led to the submission of false information to the sponsor.

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

Our investigation revealed that various procedures required by the protocol were not conducted. Specifically:

a. The protocol required that a screening EKG be obtained at visit 0. An EKG was not obtained at visit 0 for subjects: 010401 on 1/7/08; 010402 on 1/30/08; 010404 on 3/4/08; 010410 on 7/9/08; 010411 on 7/9/08; and 010412 on 7/10/08.
b. The protocol required that an EKG be obtained at visit 3. An EKG was not obtained at visit 3 for subjects: 010417 on 9/18/08; 010418 on 9/18/08; and 010421 on 10/15/08.
c. The protocol required that an EKG be obtained and that a physical exam be performed at visit 8 or at the end of treatment.
    i. An EKG was not obtained at visit 8 or at the end of treatment for subjects: 010403 on 8/6/08; 010411 on 9/28/08; 010412 on 9/29/08; 010417 on 9/30/08; 010418 on 9/30/08; and 010419 on 9/30/08.
    ii. A physical exam was not performed at visit 8 or at the end of treatment for subjects: 010411 on 9/28/08; 010412 on 9/29/08; 010417 on 9/30/08; 010418 on 9/30/08; and 010419 on 9/30/08.
d. The protocol required that study stipend payments to subjects be documented with two site personnel signatures. Only one signature was documented for subjects 010410, 010411, 010412, 010417, 010418, 010419, and 010420.

Our investigation also revealed that various procedures were either not conducted, or were not conducted by an investigator as required by the protocol. Specifically:

e. The protocol required that physical examinations be performed by an investigator (i.e., either by you, as the principal investigator, or by a sub-investigator to whom you delegated that responsibility). On the Signature Sheet and Delegation of Duties Log, you delegated the responsibility to perform physical examinations to various sub-investigators, but not to the study coordinators. For subjects 010414 on 7/29/08, and 010420 on 9/2/08, the screening Physical Examination forms contain fraudulent signatures of sub-investigators; therefore, these physical examinations do not appear to have been conducted by an investigator. The screening Physical Examination form for subject 010410 on 7/9/08 contains the signature of the study coordinator, but the responsibility to perform physical examinations was not delegated to that person.
f. The protocol required that subject eligibility be evaluated at various times. On the Signature Sheet and Delegation of Duties Log, you delegated the responsibility to determine subject eligibility to various sub-investigators, but not to the study coordinators. The Inclusion and Exclusion Criteria forms were signed by the study coordinator for subjects: 010401 on 1/7/08; 010404 on 3/4/08; 010410 on 7/9/08; 010412 on 7/10/08; and 010411 on 7/9/08. Therefore, the eligibility of these subjects does not appear to have been determined by an investigator.

Because the study coordinator falsified various study documents (as described in item

1 above, and as the study coordinator admitted in the memorandum he signed on November 10, 2008), FDA has no assurance that these procedures were performed as the Physical Examination and Inclusion and Exclusion Criteria forms appear to indicate. If these procedures were performed, there is no documentation that investigators performed them as required by the protocol and the Signature Sheet and Delegation of Duties Log.

We note that in your response to the Form FDA 483 you agreed that the study coordinator did not perform study procedures according to the investigational plan.

We acknowledge the corrective actions that you have taken to help ensure that future studies are conducted in accordance with the investigational plan. However, these corrective procedures do not specify how you will address the integrity of the investigational procedures in the other clinical investigations in which the study coordinator was involved (as indicated in the list of other studies Northstar Medical Center provided to FDA during the investigation). Moreover, regardless of your corrective actions, your failure to supervise your study coordinator led to the failure to conduct the study according to the investigational plan, and consequently to the submission of false information to the sponsor.

4. **You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].**

   The protocol required that drug disposition be documented on sponsor-provided case report forms for individual subject tracking, and Logs for master tracking.

   As discussed above, the person identified as Subject 010417 did not participate in the study, but the Subject Dispensing Log indicated that Subject 010417 was dispensed study kits numbered 1642, 2553, and 2659. Approximately 208 tablets are unaccounted for from these kits.

   We acknowledge that in your response to the Form FDA 483 you outlined the corrective actions that you have taken to prevent this type of violation from occurring in the future. However, these corrective procedures do not specify how you will address the integrity of the investigational drug product accountability in the other clinical investigations in which the study coordinator was involved (as indicated in the list of studies Northstar Medical Center provided to FDA during the investigation). Moreover, regardless of your corrective actions, your failure to supervise your study coordinator led to the failure to account for the disposition of the investigational drug, and consequently to the submission of false information to the sponsor.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational products. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, FDA asserts that you have failed to protect the rights, safety and welfare of subjects under your care, repeatedly or deliberately submitted false information to the sponsor and repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks to human subjects and jeopardized the integrity of data, and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at 301-796-3150 to arrange a conference time or to indicate your intent to respond in writing.

Should you choose to respond in writing, your written response should be forwarded within thirty (30) days of receipt of this letter.

Your reply should be sent to:

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5342
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and a representative of your choice may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The FDA's Center for Drug Evaluation and Research (the Center) will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement

of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products.

You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

To enter into the enclosed consent agreement with FDA, thereby terminating this disqualification process, you must:

(1) initial and date each page of this Agreement,
(2) sign and date the last page of this Agreement, and
(3) return this Agreement initialed, signed and dated to the signature below.

A copy of the fully executed Agreement will be mailed to you.

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

Enclosures:
#1 - Consent Agreement
#2 - 21 CFR 16
#3 - 21 CFR 312.60 and 62(a)
#4 - 21 CFR 312.70

cc

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
11/27/2009