DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Richard Holub, M.D.
Neurological Associates of Albany
760 Madison Avenue
Albany, New York 12208

Ref: 08-HFD-45-09-01

Dear Dr. Holub:

Between September 4 and October 18, 2007, Ms. Denise Terzian, 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) entitled "A Double-Blind, Phase II, Safety and Efficacy Evaluation of (b) (4) in Patients with Mild to Moderate Alzheimer's Disease," of the investigational drug (b) (4), performed for (b) (4);

- Protocol (b) (4) entitled "A Randomized, Multicenter, Double-blind, Placebo-controlled, 18-month Study of the Efficacy of (b) (4) in Patients with Mild-to-moderate Dementia of the Alzheimer's Type," of the investigational drug (b) (4), performed for (b) (4); and

- Protocol (b) (4) entitled "A 6-MONTH, Randomized, Double Blind, Placebo-Controlled, Multicenter, Safety, Tolerability, and Efficacy Study of 3 Doses of (b) (4) in Outpatients With Mild to Moderate Alzheimer's Disease Treated With a (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 ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report, the documents submitted with that report and your March 15, 2008 letter written in response to the Form FDA 483,

Inspectional Observations, 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 Ms. Terzian presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to personally conduct or supervise the investigation [21 CFR 312.60].**

   When you signed the investigator statements (Form FDA 1572) for the above-referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator. You specifically agreed to personally conduct or supervise those aspects of the study you did not personally conduct, and to ensure that all associates, colleagues, and employees assisting in the conduct of the study were informed about their obligations.

   You did not adequately supervise individuals to whom you delegated study tasks. The FDA inspection revealed that for protocol (b) (4) your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trials were conducted according to the signed investigator statement and applicable regulations. Your lack of adequate oversight resulted in protocol violations, inadequate drug accountability, inadequate informed consent, study records (informed consent documents) not being available for the FDA inspection, and inadequate and inaccurate case histories, as noted in items 2-6 below.

2. **You failed to ensure that the investigation was conducted according to the signed investigator statement and investigational plan [21 CFR 312.60].**

   a. You failed to ensure that the study was conducted in accordance with the protocol. Examples include, but are not limited to, the following:

      Regarding Protocol (b) (4)

      i. The subject numbers were not sequentially assigned to all subjects screened at the site as required by the protocol. Examples include, but are not limited to, the following:
         1. Subject (b) (6) screened on April 22, 2005, was the third subject screened for the study; however, the subject was assigned #747-004.
         2. Subject (b) (6) screened on May 12, 2005, was the fourth subject screened for the study; however, the subject was assigned #747-003.
      ii. Protocol-required magnetic resonance imaging or computer tomography scan, Mini-Mental State Examination, and Modified Hachinski test were not performed for subjects 747-006, 747-007, and 747-008.

iii. A unique six-digit subject number was not assigned to each subject as required by the protocol. Specifically, subject (b) (6) and (b) (6) were both assigned number 747-005.
iv. The protocol excluded potential subjects who were taking Aleve (naproxen) medication one (1) month prior to the screening visit. The Medical Information Sheet for subject 747-004 at screening documents that the subject was currently taking Aleve; however, the subject was randomized in violation of the protocol. In addition, protocol-required physical exams for day 43 and laboratory test for day 64 were not performed for this subject.

Regarding Protocol (b) (4)

v. Protocol-required clinical laboratories assessments and (b) (6) were not performed for subject 084-009 at Visit #2.
vi. Protocol-required physical examination was not performed for subject 084-002 at Visit #7.

b. Study coordinators who administered the informed consent, determined subject eligibility and dispensed study drug were not listed on the Form FDA-1572, Statement of Investigator, for protocols (b) (4) and (b) (4). By performing these significant study activities, the study coordinators should have been listed on the Form FDA 1572s as subinvestigators.

3. You failed to maintain adequate and accurate records for disposition of the investigational drug [21 CFR 312.62(a)].

Regarding protocol (b) (4), study subjects were distributed study medication kits not assigned to them.

Specifically, the (b) (4) randomization confirmations indicated that subject 747-002 was assigned kit number 0495, subject 747-003 was assigned kit number 0655, and subject 747-004 was assigned kit number 0582. However, study medication labels (blister card labels) revealed the following:

a. A blister card label for kit number 0582 was found identified as distributed to subject 747-002 instead of subject 747-004;
b. Three study medication labels for kit number 0495 was found identified as distributed to subject 747-003 instead of subject 747-002; and
c. Twelve study medication labels for kit number 0495 was found identified as distributed to subject 747-004 instead of subject 747-002.

4. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].

21 CFR 50.20 requires that except as provided in sections 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by FDA

regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. In addition, the FDA regulations require that informed consent be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent [21 CFR 50.27(a)].

Regarding protocol (b) (4)

a. Subject 2006 had study assessments and procedures performed during the screening visit on February 2, 2007; however, the subject did not sign the informed consent form approved by the Institutional Review Board (IRB) until May 18, 2007.

b. Subject 2005 had study assessments and procedures performed for protocol (b) (4) on January 18, 2007 at the screening visit; however, the subject signed a consent form for another study, protocol (b) (4) and did not sign the consent form for participation in protocol (b) (4) until March 6, 2007.

Regarding protocol (b) (4)

c. During the FDA inspection you were not able to provide signed informed consent documents for subject 747-007. You told the FDA investigator that this subject signed an informed consent document, but you could not locate the document. Inspection revealed that the caregiver could not recall informed consent document being signed.

5. **You failed to retain records required to be maintained by the clinical investigator under 21 CFR part 312 for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified [21 CFR 312.62(c)].**

Regarding protocol (b) (4), during the FDA inspection you were not able to provide signed informed consent documents for subjects 747-005 and 747-006. You told the FDA investigator that these subjects signed informed consent documents, but you could not locate the documents.

6. **You failed to maintain adequate and accurate case histories that record all observations and data pertinent to the investigation [21 CFR 312.62(b)].**

Examples include, but are not limited to, the following:

Regarding protocol (b) (4)

a. No Case Report Forms were completed for subjects 747-005 (b) (6)), 747-006, 747-007, and 747-008.

b. Subject (b) (6) was assigned number 747-005, but was identified with number 747-007 on the laboratory form dated July 8, 2005, and number 747-008 on the laboratory report dated July 13, 2005.

In your March 15, 2008 written response to the Form FDA 483 you stated that the Form FDA 483 items were a reflection of the failure of a few clinical research coordinators to adhere to the established Standard Operating Procedures (SOPs). You mentioned correctives actions that will be taken to assure that such errors are not repeated. These include the process used to select, train, and manage research staff, and SOPs governing the day-to-day work of the research division. The response does not address oversight of the research activities by the clinical investigator and appears to place the burden of responsibility for the research activities on the study staff. Although hiring qualified staff and providing training may help with the performance of study related activities, this does not substitute for your responsibilities as the clinical investigator to supervise those aspects of the studies you delegate to research staff.

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 on-going 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 or will be taking 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 Lewin, 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 Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
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Office of Compliance
Center for Drug Evaluation and Research
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10903 New Hampshire Avenue
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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

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
10/01/2008