DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Alan Rapoport, M.D.
84 Farms Rd.
Stamford, CT 06903

Ref: 08-HFD-45-1001

Dear Dr. Rapoport:

Between May 01 and June 05, 2007, Ms. M. Patricia Murphy and Ms. Diane Thibodeau, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of clinical investigations (protocol [ ] entitled "A Phase III Study of the Efficacy and Safety of [ ] in Patients with Mild to Moderate Alzheimer's Disease," and protocol [ ] entitled " An Open-Label Extension of the Phase III Study [ ] with [ ] in Patients with Alzheimer's Disease") of the investigational drug [ ] performed for [ ] At the time you performed the studies you were working at the New England Center for Research doing business as the New England Research Institute, 778 Long Ridge Rd., Stamford, CT 06902.

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.

From our review of the establishment inspection report, the documents submitted with that report and your August 3, 2007, 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. We are aware that at the conclusion of the inspection, Ms. Murphy and Ms. Thibodeau presented and discussed with your sub-investigator, Ms. [ ] Form FDA 483, Inspectional Observations. Ms. Murphy also discussed the Form FDA 483, Inspectional Observations with you via telephone and mailed a copy to you. We wish to emphasize the following:

1. **You failed to ensure that the investigations were conducted according to the signed investigator statement [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.

a. You failed to adequately supervise individuals to whom you delegated study tasks. The FDA inspection revealed that 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 office calendar indicates that you were away from the office on forty (40) of the ninety seven (97) subject visit dates for protocol[ ] In addition, you told the FDA Investigator that you did not review study records on a regular basis. Your failure to provide adequate oversight resulted in source documents containing inaccurate information and inadequate informed consent documentation as outlined in items 2 and 3 below.

b. You failed to list the names of all sub-investigators who would be assisting in the conduct of the investigation, as required by the Form FDA 1572. According to the study records, the study coordinator administered the Alzheimer's Disease Assessment Scale, cognitive subscale (ADS-cog), which is used for the primary efficacy endpoint for protocol[ ] The study coordinator also signed her name as the person who reviewed the subjects' visits on the source documents. By performing these significant study activities, the study coordinator should have been listed on the Form FDA 1572 as a sub-investigator.

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

a. Your office calendar indicates that you were not present in the office on dates when your name was signed as the investigator who completed the study related tasks on multiple source documents, including physical exam forms, Hachinski Ischemia Scale, Dementia with Lewy Bodies Assessment forms, and laboratory reports for protocol[ ] As you were not available to complete examinations and assessments of subjects on those dates, and given that your name is signed on documents representing that you had, the documents contain inaccurate information. Examples include, but are not limited to, the following:

i) According to your office calendar, you were away from the office for the following subjects' visit dates: 154[ ](10/4/04, 6/29/05, 10/3/05, and 4/26/06); 155[ ] (10/4/04 and 11/1/04); 156[ ](11/16/04, 12/14/04, 1/18/05, 10/20/05, and 1/25/06); 166[ ](10/27/04, 12/20/04, and 1/25/05); 167[ ](11/1/04 and 12/21/04); 168[ ](2/9/05 and 5/9/05); 400[ ](11/1/04, 12/20/04, 2/23/06, and 5/17/06); 401[ ](12/21/04, 1/20/05, 12/14/05, and 3/8/06); 402[ ](12/15/04 and 3/14/05); 403[ ](1/3/05, 3/30/05, 11/3/05, and 8/3/06); 404[ ](1/3/05, 2/7/05, 3/9/05, 5/11/05, 8/4/05, 11/17/05, 1/25/06, and 5/17/06); and 405[ ] (3/14/05, 3/29/05, 4/21/05, 9/29/05, 4/5/06, and 9/25/06). Your name is signed on the source documents as the investigator who completed the physical exams at those

visits.

ii) According to your office calendar, you were away from the office for the following subjects' visit dates: 155[ ](10/4/04); 403[ ](1/3/05); 404[ ](1/3/05); and 405[ ](3/14/05). Your name is signed on the source documents as the investigator who completed the Hachinski Ischemia Scale and the Dementia with Lewy Bodies Assessments at those visits.

iii) Your name is signed on the source documents as the investigator who reviewed laboratory reports and ECG reports for subjects on the following dates: 154[ ] (9/22/04, 4/21/05 and 4/26/06); 155[ ](7/11/05, 10/6/05, and 1/18/06); 168[ ] (10/28/04, 2/14/05 and 5/11/05); 400[ ](5/26/05); 402[ ](3/17/05); 403[ ] (5/9/05 and 11/7/05); 404[ ](1/3/05, 5/19/05 and 8/4/05); and 405[ ] (4/10/06). According to your office calendar, you were away from the office on those dates when the above mentioned laboratory and ECG reports were reviewed.

iv) Your name is signed on reports of serious adverse events for subject 168 on 10/11/05 and 11/16/05. According to your office calendar, you were away from the office on those days.

b. For protocol[ ]we cannot determine which study records were signed by you. You stated that you did not back date any source documents. Your sub-investigator, Ms. [ ]stated that she did sign your name to documents on days that you were not in the office. However, you stated that you signed a physical exam source document for subject 404[ ]on May 17, 2006. Your sub-investigator, Ms.[ ] stated that she signed your name to the same source document. According to your office calendar, you were in Italy on May 17, 2006.

c. The study records do not accurately reflect the person who conducted the study activities. Protocol[ ]requires a causality assessment by the investigator in terms of relationship to study medication for purposes of reporting adverse events. For subjects 154[ ] 155[ ], 156[ ]166[ ]167[ ]168[ ]400[ ]401[ ] 402[ ]403[ ]404[ ]and 405[ ]the study coordinator's initials are on the adverse event logs, which appear to indicate that the study coordinator performed the causality assessment. However, you told the FDA Investigator that you made the causality determinations.

The investigation revealed that your staff signed your name on many of these documents (i.e. that the signature of your name was not written by you). You told the FDA Investigator that you were not aware that your name was signed by anyone other than yourself until it was brought to your attention by the sponsor's monitors. As the clinical investigator who signed the Form FDA 1572, you are responsible for oversight of activities performed by the study staff.

We note that in your August 3, 2007, letter written in response to the Form FDA 483, Inspectional Observations, you acknowledged that your name was signed on documents by Ms. [ ]and the study coordinator. You also mentioned that the office calendar may not be

completely accurate in reflecting days that you were out of town. You also stated that there were days in which you were in the office for several hours before leaving and that you may have conducted examinations on those days. However, you did not provide any supporting documentation to reflect that you were present in the office on days when your calendar indicates that you were away from the office.

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

   Informed consent must be documented by the use of a written consent form approved by the Institutional Review Board (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. For subject 155 enrolled in protocol[ ] the "yes" block is checked in response to the question "Is the subject required to have a Legally Authorized Representative (LAR)" on the demographic section of the screening form. However, the LAR for this subject did not sign the informed consent form. We note that in your August 3, 2007, letter written in response to the Form FDA 483, Inspectional Observations, you mentioned that it is your recollection that subject 155 did not require a legally authorized representative, and the "yes" box was erroneously checked. You did not provide any evidence to support your statement.

   b. The handwritings on the consent forms indicate that one person dated both the signature of the subjects and the signature of the person conducting the consent/addendum discussion. Examples include, but are not limited to, the following subjects' consent forms for protocol[ ]154[ ](1/4/04, 6/29/05, and 7/27/06); 155[ ](7/5/05), 156[ ](10/5/04, 1/18/05, and 7/19/05); 166[ ](10/27/04, 4/26/05, 7/26/05, and 4/25/06); 167[ ](10/19/04, 11/07/04, and 5/25/05); 168[ ](10/26/04 and 5/9/05); 400[ ](5/23/05); 401[ ](10/26/04, 6/7/05, and 5/30/06); 402[ ](12/15/04 and 12/15/05); 403[ ](1/3/05, and 2/15/06), and 405[ ](3/14/05 and 7/5/05). Examples include, but are not limited to, the following subjects' consent forms for protocol[ ]155[ ](5/31/06); and 401[ ](5/30/06).

In your August 3, 2007, letter written in response to the Form FDA 483, Inspectional Observations, you stated that if you participate in a clinical study in the future you will by personal attention and training of staff, seek to ensure the observations do not recur. We acknowledge your assurance, but note that your response did not contain a detailed outline of procedures or processes that would be implemented to prevent the future occurrence of these observations.

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 (240) 276-8829; FAX (240) 276-8844. 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, HFD-46
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Acting Director
Division of Scientific Investigations, HFD-45
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 Ball
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