DEPARTMENT OF HEALTH & HUMAN SERVICES

M3770N

WARNING LETTER

Food and Drug Administration
Rockville MD 20857

MAY 24 2000

Ref: 00-HFD-45-0401

CERTIFIED MAIL - RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

Anne L. Macek, M.D.
Howard S. Cummins, Ph.D.
Institute for Advanced Clinical Research
7900 High School Road
Elkins Park, Pennsylvania 19027

Dear Drs. Macek and Cummins:

Between February 14 and 24, 2000, Ms. Susan F. Laska, representing the Food and Drug Administration (FDA), met with Dr. Macek to review your conduct as co-investigators of the following clinical studies of the investigational drug[ ]performed for[ ]

Protocol[ ]"Placebo-Controlled Evaluation of[ ]in the Treatment of Alzheimer's Disease: Safety and Efficacy under a Slow Titration Regimen"

Protocol[ ]"Safety and Efficacy of[ ]during Withdrawal in the Treatment of Alzheimer's Disease"

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and documents provided by the sponsor, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices. We note that at the conclusion of the inspection, Ms. Laska presented and discussed with Dr. Macek the items listed on Form FDA 483, Inspectional Observations. The outcome of the FDA inspection raises serious concerns regarding the quality of your clinical research. We wish to emphasize the following:

SUMMARY OF VIOLATIONS RELATED TO PREPARING AND MAINTAINING ADEQUATE AND ACCURATE CASE HISTORIES [21 CFR 312.62(b)]

During the inspection, our field investigator noticed names in the upper right corner of various pages of your office appointment book. When asked about the purpose of this, Dr. Macek stated that these entries represented office staff members who were not in the office on the dates reflected. Given this explanation, your office records indicate that Dr. Macek was not in the office on October 22, 1998, or June 1, 1999. We note the following discrepancies in study[ ]documentation:

For subject A73377, there are a Visit 1 progress note, physical and neurological examination pages of the CRF, and medical/surgical history page of the CRF, all signed by Dr. Macek on October 22, 1998.

For subject A73623, there is one Visit 5 physical examination page of the CRF signed by Dr. Macek on June 1, 1999, with a diagonal line across the page and the word "error" above the date of June 8, 1999. In addition, what appear to be Dr. Macek's initials are noted below the word "error" and next to the date of June 8, 1999. There is a second version of this page of the CRF, which was also signed by Dr. Macek on June 1, 1999, with a diagonal line across the page and the words "not done."

For subject A73624, there are two versions of a final visit physical examination page of the CRF dated June 1, 1999, both containing a diagonal line across the page and the words "not done." Both documents bear Dr. Macek's signature dated June 1, 1999.

For subject A73592, there are two versions of a Visit 5 physical examination page of the CRF signed by Dr. Macek on June 1, 1999, with a diagonal line across each of the pages and the words "not done." In addition, one of the pages contains what appear to be Dr. Macek's initials next to the words "not done."

Based upon Dr. Macek's explanation noted above regarding appointment-book entries, your office records indicate that your sub-investigator Anita Cummins was not in the office on April 14, 1999, or June 1, 1999. We note the following discrepancies in study[ ] documentation:

For subject A73377, final visit pages of the CRF for caregiver and subject interviews were reported to have been completed by Ms. Cummins on April 14, 1999.

For subject A73592, final visit pages of the CRF for caregiver and subject interviews and a final visit page of the CRF for a[ ]plus assessment reflect completion by Ms. Cummins on June 1, 1999. In addition, the final visit page of the CRF for June 1, 1999, shows completion of the caregiver interview although a progress note written on that same date states that this caregiver was unable to attend this visit. Furthermore, a paragraph of this progress note initially leads one to believe that the caregiver was present, by use of the term "Caregiver reports. . .". The progress note later states, in the same paragraph, that the caregiver was unable to attend this visit.

For subjects A73623 and A73624, final visit pages of the CRF for caregiver and subject interviews were reported to have been completed by Ms. Cummins on June 1, 1999.

SUMMARY OF PROTOCOL VIOLATIONS (21 CFR 312.60)

For subjects A73592, A73623, and A73624, you failed to conduct physician visits and perform physical examinations for the final visit in study[ ]and at Visit 1 in study[ ]

For subject A73372, you failed to conduct a physician visit and perform a physical examination for Visit 5 in study

Subject A73962 was inappropriately enrolled in study because this subject failed to have a 60-day washout of the drug Aricept prior to enrollment in this study.

SUMMARY OF VIOLATIONS RELATED TO DRUG ACCOUNTABILITY [21 CFR 312.62(a)]

You failed to return to the sponsor or properly dispose of 14 boxes of study drug from study This drug supply, which was intended for distribution to 14 subjects at Visit 4, was noted to still be in your possession eight months after this study was terminated. It is not clear what study medication, if any, these 14 subjects received at Visit 4.

Because of the nature of the violations of FDA regulations discussed above, we request that you notify us, in writing, within 15 working days of your receipt of this letter of the actions that you have taken or plan to take to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in further regulatory action, without further notice.

If you have any questions, please contact Dr. Antoine El-Hage, at (301)594-1032, FAX (301)827-5290. Your written response and any pertinent documentation should be addressed to:

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely,

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research