DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 29, 2002

William H. Parker, Ph.D.
Vice Chancellor for Research
University of California, Irvine
155 Administration Building
Irvine, CA 92967

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1305

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease
Principal Investigator: Ruth A. Mulnard, R.N., D.N.Sc.
IRB Protocol #: #95*270
HHS Project Number: U01-AG10483
IND#: 48,114

Research Publication: Estrogen Replacement Therapy for Treatment of Mild to Moderate Alzheimer Disease: A Randomized Controlled Trial (Mulnard, et al. JAMA. 2000;283:1007-1015)

Dear Dr. Parker:

The Office for Human Research Protections (OHRP) has reviewed the University of California, Irvine's (UCI's) March 21, 2002 report that was submitted in response to OHRP's February 8, 2002 letter regarding the above-referenced research.

Based upon its review, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(b) stipulate that in order to approve research, the Institutional Review Board (IRB) shall determine

that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of the subjects. In its February 8, 2002 letter, OHRP expressed concern that the UCI IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that UCI has adequately responded to this concern. Furthermore, OHRP acknowledges that the UCI IRBs have implemented procedures to ensure consideration of additional safeguards for subjects who may be vulnerable as a result of impaired mental capacity.

OHRP notes that HHS regulations at 45 CFR 46.109(e) stipulate that IRBs have the authority to observe or have a third party observe the consent process and the research. OHRP encourages IRBs to use this authority.

(2) HHS regulations at 45 CFR 46.116(a)(2) require that when seeking informed consent, each subject be provided with a description of any reasonably foreseeable risks and discomforts. In its February 8, 2002 letter to UCI, OHRP noted that the informed consent document for the above-referenced research was not revised to include a description the risk of thromboembolic disease until 8 months after the UCI IRB received the third of three reports of subjects experiencing thromboembolic events that were believed by the investigators to be probably or possibly related to the research interventions.

OHRP finds that it would have been appropriate for the UCI IRB to more promptly require modification of the informed consent document for the above-referenced research.

Corrective Action: OHRP acknowledges that following an on-site review by the Office for Protection from Research Risks (OPRR), OHRP's predecessor office, in July 1998, UCI implemented new procedures for IRB review of serious adverse event reports that adequately address the above finding.

(3) HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, each subject be provided with, among other things, a description of the procedures to be followed and identification of any procedures which are experimental. OHRP finds that the informed consent documents approved by the UCI IRB for the above-referenced research failed to include a description of the procedure for having the subject's caregiver fill out quality-of-life and pharmacoeconomic questionnaires related to the subject's condition and care.

Corrective Action: OHRP acknowledges that (i) the research has been completed; (ii) since the above-referenced research was reviewed by the UCI IRB, UCI has implemented numerous steps to improve its system for protecting human subjects following OPRR's on-site evaluation

in 1998 that adequately address the above finding.

(4) OHRP finds that UCI has adequately addressed the additional concerns raised by OHRP in its February 8, 2002 letter.

As a result of the above determinations, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

At this time, OHRP provides the following additional guidance in response to UCI's March 21, 2002 report:

(5) HHS regulations at 45 CFR 46.116(a)(4) require that when seeking informed consent, each subject be provided with a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. In its February 4, 2002 letter to UCI, OHRP expressed concern that the IRB-approved informed consent documents for the above-referenced research did not describe the alternative of receiving estrogen replacement therapy outside of the research.

UCI's report stated the following in response:

> "As [estrogen replacement therapy] was not an approved treatment for [Alzheimer's disease (AD)] at the time of the trial, it would have been improper for site investigators to suggest, or for consent documents to indicate, that AD subjects could also seek therapeutic benefit for their Alzheimer's disease through use of estrogen outside of the study."

OHRP acknowledges UCI's statement. OHRP also notes that it may have been appropriate to disclose in the informed consent document the alternative of receiving estrogen replacement therapy outside of the research context for known standard indications in the study population (i.e., treatment of menopausal vasomotor symptoms, atrophic vaginitis, and osteoporosis).

Furthermore, where a particular marketed drug is being used by healthcare providers to treat patients for an indication which has not been approved by the FDA, it may be appropriate to disclose that use as an alternative treatment to subjects in the informed consent document.

OHRP appreciates the commitment of UCI to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Ms. Suzanne Rivera, Director, Research Conduct Administration, UCI
Dr. Robert H. Blanks, Chairperson, IRB-01, UCI
Dr. David Imagawa, Chairperson, IRB-02, UCI
Dr. Ruth Mulnard, Chairperson, IRB-03, UCI
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
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Mr. George Gasparis, OHRP
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Mr. Barry Bowman, OHRP