DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 25, 2002

Dr. Barry M. Klein
Vice Chancellor for Research
402 Mrak Hall
One Shields Avenue
University of California
Davis, California 95616

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1325

Research Project: A Multicenter, Double-Blind, Placebo-Controlled Study of Estrogen Replacement Therapy in Patients with Mild to Moderate Alzheimer's Disease
Principal Investigator: Dr. William J. Jagust
HHS Project Number: U01-AG10483
IRB Project Numbers: 97-528

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. Klein:

The Office for Human Research Protections (OHRP) has reviewed the University of California, Davis's (UC Davis's) April 16, 2002 report that was submitted in response to OHRP's February 7, 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 7, 2002 letter, OHRP expressed concern that the UC Davis IRB may have failed to ensure that this requirement was satisfied for the above-referenced research.

OHRP finds that the UC Davis has adequately responded to this concern. Furthermore, OHRP acknowledges that the UC Davis's IRB considers additional safeguards for subjects who may be vulnerable as a result of impaired mental capacity.

(2) 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 IRB-approved informed consent documents failed to describe the procedures for having the subject's caregiver fill out quality-of-life and pharmacoeconomic questionnaires related to the subject's condition and care.

OHRP acknowledges (i) that the research has been completed; and (ii) UC Davis's IRB has acknowledged that it failed to include a description of these procedures in the consent document.

(3) 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 letter of February 7, 2002, OHRP expressed concern that the revised informed consent documents for the above referenced study did not further describe the potential clinical consequences of thromboembolic events. Further, OHRP questioned whether the UC Davis IRB required investigators to provide the one subject enrolled in the study with information regarding the risk of thromboembolic disease, following the IRB review and approval of a modification to include the complication of thromboembolic phenomena in the consent form.

OHRP finds that the UC Davis IRB has adequately responded to this concern. Furthermore, OHRP acknowledges that the UC Davis's response that the revised consent form detailing the risk of thromboembolic events associated with estrogen use was signed by the single subject enrolled at UC Davis.

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 UC Davis's April 16, 2002 report:

(4) 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 7, 2002 letter to UC

Davis, 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 protocol.

In response, UC Davis stated that estrogen replacement therapy was not an approved treatment for Alzheimer's disease and therefore "the investigator could not properly suggest off-study estrogen replacement therapy as a tested and effective alternative treatment."

OHRP acknowledges UC Davis'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 Food and Drug Administration (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 UC Davis to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Leslie K. Ball, M.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Mr. David Holt, Director, Office of Human Research Protection
Dr. Amy Ernst, Chair IRB A, UC Davis
Dr. Neil Flynn, Chair IRB B, UC Davis
Dr. William Jagust, Principal Investigator, UC Davis
Commissioner, FDA
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