DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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August 9, 2005

Myron Rosenthal, Ph.D.
Senior Associate Dean and Director, Human Subjects Research Office
Faculty/Professional Affairs
University of Miami
Park Plaza East, Suite M
Miami, FL 33136

RE: Human Research Subject Protections Under Federalwide Assurance FWA-2247

Research Project: A 4-Year, Double Blind, Randomized, Placebo-Controlled Study of Atorvastatin as Preventative of CHD End Points in Patients with (Type II) Noninsulin-Dependent Diabetes Mellitus
Principal Investigator: Dr. Ronald Goldberg
Project Number: 981-71-27

Dear Dr. Rosenthal:

The Office for Human Research Protections (OHRP) has reviewed the University of Miami's (UM) August 19, 2003 and June 8, 2005 reports responding to allegations of noncompliance regarding research involving atorvastatin, as well as UM's November 10, 2004 and May 12, 2005 reports of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

Based upon its review, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the institutional review board (IRB) review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that the following protocol changes were implemented in the atorvastatin protocol before IRB approval was

obtained:

(a) Enrollment of subject TKB even though he met the exclusion criterion of "participation in another clinical study concurrently or within 30 days prior to screening for the present study." TKB was screened for the study referenced above on September 15, 1997, but had just completed another study with Dr. Goldberg on August 18, 1997.

(b) Implementation of an incentive program for subjects (provision of glucose testing strips, calling cards, and a subscription to a magazine) prior to IRB review and approval of such a program.

Required Action: By September 14, 2005, please provide a corrective action plan to ensure that the UM IRBs review and approve proposed changes in a research activity prior to their implementation.

(2) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP finds that the informed consent document approved by the IRB for the retinopathy substudy included complex language that would not be understandable to all subjects, such as "secreted," "superficial lesion," "visual acuity."

Required Action: By September 14, 2005, please provide a corrective action plan to ensure that the UM IRBs approve informed consent documents written in language understandable to the subjects.

(3) OHRP finds that the informed consent documents reviewed and approved by the IRB for the retinopathy substudy failed to include and/or adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts.

(b) Section 46.116(a)(3): A description of any benefits to the subject or others that may *reasonably* be expected from the research.

(c) Section 46.116(a)(4): A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(d) Section 46.116(a)(5): A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

(e) Section 46.116(a)(7): An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights (should include someone other than the investigator), and whom to contact in the event of a research-related injury to the subject.

(f) Section 46.116(a)(8): A statement that participation is voluntary, refusal to

participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Required Action: By September 14, 2005, please provide a corrective action plan to ensure that the UM IRBs approve informed consent documents that adequately address the elements required by HHS regulations at 45 CFR 46.116(a) unless appropriately waived by the IRB.

(4) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364-60367. OHRP finds that continuing review in the atorvastatin protocol on September 10, 2001 was conducted in an expedited manner even though it was not eligible for expedited review. OHRP notes that the IRB indicated that the study was reviewed under expedited category 8: Continuing review of research previously approved by the convened IRB as follows: (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or (b) where no subjects have been enrolled and no additional risks have been identified; or (c) where the remaining research activities are limited to data analysis. However, it appears from records provided to OHRP that subjects were still receiving study medication, and therefore all subjects had not completed all research-related interventions.

Required Action: By September 14, 2005, please provide a corrective action plan to ensure that the UM IRBs utilize the expedited review mechanism only for the specific research categories published in the Federal Register at 63 FR 60364-60367.

(5) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB chair or another IRB member designated by the chair, continuing review must occur no more than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date on which the IRB chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP finds that the IRB failed to conduct continuing review of research at least once per year for numerous studies. The initial review in the atorvastatin protocol was conducted on September 16, 1996, with continuing reviews being conducted on September 29, 1997 and November 2, 1998. In addition, OHRP notes that roughly one third of all active protocols at UM have expired, including over 200 that have not been reviewed since 2004 or earlier, and protocols that have not been reviewed since 1999 and 2001. Many investigators have not been notified that their protocols have expired.

The IRB and investigators must plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the IRB, or if the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interests of subjects already enrolled to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval.

Required Action: By September 14, 2005, please provide a corrective action plan to ensure that the UM IRBs conduct continuing review of research at intervals appropriate to the degree of risk, and not less than once per year. OHRP acknowledges that, while the UM IRBs are being reconstructed, a commercial IRB is reviewing all UM human subjects research. Please provide OHRP with an update on the status of the following corrective actions outlined in UM's June 24, 2005 letter: (a) Sending letters to investigators to inform them that they must stop all human subjects research activity in protocols that have expired, unless it is in the best interests of the subjects to continue; and (b) implementation of a system to send investigators notices that warn them of the expiration dates of protocols before the protocols expire.

(6) OHRP finds that the informed consent document reviewed and approved by the IRB for the atorvastatin protocol failed to adequately address a complete description of the procedures to be followed, and identification of any procedures which are experimental, as required by HHS regulations at 45 CFR 46.116(a)(1). In specific, the protocol included a six-week single-blind placebo-baseline period, during which all subjects were given a placebo; however, the informed consent document indicated that subjects would be randomized to either placebo or atorvastatin at this point. OHRP acknowledges that the single-blind placebo-baseline period intended that subjects be deceived about possibly receiving atorvastatin to assess "qualification for randomization"; however, there is no evidence that the IRB approved a waiver of informed consent for this single-blind phase, or that subjects were later informed about the deception.

Required Action: By September 14, 2005, please provide a corrective action plan to ensure that the UM IRBs approve informed consent documents that adequately address the elements required by HHS regulations at 45 CFR 46.116(a) unless appropriately waived by the IRB.

(7) [Redacted]

(8) It was alleged that the investigators failed to obtain legally effective informed consent prior to initiating the above-referenced human subjects research, as required by HHS regulations at 45 CFR 45.116. In specific, it was alleged that subject TKB was not provided with proper initial informed consent, and that his signature was forged on two informed consent documents.

OHRP acknowledges UM's statements that:

> (a) Review of documentation for all subjects that underwent study-specific testing indicated that informed consent was obtained from all subjects prior to initiation of study-specific procedures.
>
> (b) The study file contains the initial IRB-approved informed consent document as signed by TKB dated September 15, 1997, and that this signature appears to be similar to subsequent signatures on various documents.
>
> (c) The principal investigator stated that for subject TKB and all enrolled subjects, informed consent was obtained under the supervision of the principal investigator, co-principal investigator, and/or study coordinators in accordance with the IRB procedures, policies, and guidelines current at the time informed consent was obtained.

Based on the above, OHRP is unable to make a finding on this matter.

(9) It was alleged that the investigators failed to seek consent under circumstances that minimize the possibility of coercion or undue influence, as required by HHS regulations at 45 CFR 46.116.

OHRP acknowledges UM's statements that:

> (a) The principal investigator stated that for subject TKB and all enrolled subjects, informed consent was obtained under the supervision of the principal investigator, co-principal investigator, and/or study coordinators in accordance with the IRB procedures, policies, and guidelines current at the time informed consent was obtained.
>
> (b) The documents indicate that subjects received either glucose strips or a calling card at the year 3 visit, and that subject TKB received a six-month supply of glucose strips. UM does not believe this compensation to be coercive.

Based on the above, OHRP is unable to make a finding on this matter.
(10) It was alleged that the informed consent documents for the above-referenced study failed to include an adequate description of the reasonably foreseeable risks and discomforts, as required by HHS regulations at 45 CFR 46.116(a)(2). In specific, it was alleged that the informed consent for this study did not fully disclose known side effects,

such as possible liver damage.

OHRP acknowledges UM's statements that the original and all subsequent versions of the approved informed consent document specifically address the possibility of liver impairment, as well as other known side effects of atorvastatin. The informed consent document stated, "This class of drug has been associated with abnormal liver function tests, hepatitis, jaundice, loss of appetite, vomiting, allergic reactions, pancreatitis, mental disturbances, sleep disturbances and nerve dysfunction."

As a result, OHRP finds that the above allegation was not substantiated.

(11) It was alleged that the investigators failed to ensure that risks to subjects were minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose the subjects to risk, as required by HHS regulations at 45 CFR 46.111(a)(1). In specific, it was alleged that subject TKB was not provided with liver tests according to the informed consent document; that his complaints of diarrhea after taking the study medication were consistently ignored by the research coordinator; that his elevated liver enzymes were ignored by the research coordinator; he was not closely monitored for liver damage, as required by study protocol and the informed consent document; that he was pressured not to see a doctor for his side effects; that despite being hospitalized due to liver failure, kidney failure, and pancreas failure and while waiting for a liver transplant, he was still being called to continue taking the study medication; that the study coordinator and the sponsor refused to tell the doctors the composition of the study medication so that they could treat TKB upon hospitalization for liver failure and jaundice; and that the IRB failed to monitor the study.

OHRP acknowledges UM's statements that:

> (a) The study chart and case report form for subject TKB indicate the principal investigator followed the study protocol with regard to "safety clinical laboratory" evaluations, with the exception of visit T13; and the documentation indicates that TKB did not keep the appointment for this study visit.
>
> (b) The case report form for TKB's October 16, 2000 visit indicates that subject TKB stated that he took the last dose of study medication on February 19, 2000, the day before he was hospitalized.

OHRP acknowledges that research notes from July 8, 1998 indicated that TKB complained of diarrhea and had discontinued medications; the plan indicated, "1) check LFT's, chem 7, CBC; 2) push PO fluids & eat blandly; 3) if not resolved f/u w/PCP." Research notes from December 8, 1998 indicated that TKB indicated diarrhea had resolved July 10, 1998, and that he had discontinued medications during episodes of diarrhea. Research notes on June 1, 1999 indicated that TKB complained of diarrhea December 26, 1998 to January 9, 1999 and February 12-16, 1999. The notes for this visit indicate that TKB took Imodium for the diarrhea, and during the diarrhea episodes he stopped taking the study medication. Research notes from December 1, 1999 indicated

that TKB complained of diarrhea July 30 to August 7, 1999 and September 2-16, 1999, during which he indicated that he stopped taking the study medication. Research notes from February 2, 2000 stated, "Received phone call from Dr. X...Requesting additional information on medications and unblinding for study med. [Sponsor contact] informed of request and Dx liver failure possible....[Sponsor contact] called. I will provide Dr. X with phone # for [Sponsor contact] as per his request." Research notes from June 23, 2000 stated, "called patient's home and left message on answering machine regarding missed study visit 6/1/00 and to inquire about health status since his liver transplant. If I do not hear from him in 1 week I will send a certified letter to last known address." Research notes from September 15, 2000 stated, "called pt to come in for final visit and return study med. No answer of telephone, message left. Certified letter set [*sic*] out to pt requesting call to make appt. for return of study med. and final visit."

Based on the above, OHRP is unable to make a finding on this matter.

By September 14, 2005, please provide responses to the corrective actions above.

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

Sincerely,

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight

cc: Dr. Steven Ullman, Vice Provost for Faculty Affairs, UM
Dr. Leo Twiggs, Assistant Vice Provost, Human Subjects Research Office, UM
Dr. Angela Bowen, President, Western IRB
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Lana Skirboll, Director, Office of Science Policy, NIH
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Ms. Shirley Hicks, OHRP
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