DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Willa A. Hsueh, M.D.
David Geffen School of Medicine at UCLA
900 Veteran Avenue, Suite 24-130
Los Angeles, CA 90095

Ref: 08-HFD-45-0503

Dear Dr. Hsueh:

Between September 4 and October 9, 2007, Ms. Diane C. Van Leeuwen, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of the following clinical investigations:

> Protocol #[ ]"Impact of Rosiglitazone on Cardiac Fibrosis, Function and Atherosclerosis in Cardiac Transplant Patients with Carbohydrate Intolerance", of the investigational drug rosiglitazone; and
>
> Protocol #[ ]Effect and Action in Diabetes[ ] Effect on Glycemic Control of[ ]in Combination with Rosiglitazone plus Metformin versus Rosiglitazone plus Metformin in Type 2 Diabetes (A Twenty-Six Week Double-Blind Parallel Trial to Investigate Safety and Efficacy)", of the investigational drug[ ]

We note that you were the sponsor-investigator for protocol[ ]and[ ] was the sponsor of protocol[ ]

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 participating in those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your October 22, 2007 written response to Form FDA 483, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Van Leeuwen presented and

discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

Sponsor Violations

1. **You failed to monitor the progress of a clinical investigation being conducted under an IND [21 CFR 312.56(a)].**

   Our investigation revealed that protocol [ ] was not monitored. It appears that had the study been monitored as required by FDA regulations, the observations discussed below might have been prevented.

2. **Before beginning the investigation, you failed to ensure that Form FDA 1572 included the names of the sub-investigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation [21 CFR 312.53(c)(1)(viii)].**

   For protocol [ ] our investigation revealed that the following physicians had a significant role in the conduct of the investigation, but were not listed on Form FDA 1572 as sub-investigators: [ ] Although Dr. [ ] signed Form FDA 1572 for protocol [ ] as the sponsor-investigator of protocol [ ] you were responsible for ensuring that you had obtained a signed investigator statement listing the names of the subinvestigators who would be assisting the investigator in the conduct of the investigation.

Investigator Violations

3. **You failed to adequately supervise the investigations [21 CFR 312.60].**

   When an investigator signs an investigator statement, he or she agrees to take on the responsibilities of a clinical investigator at his or her site. You signed Form FDA 1572 for protocol # [ ] We note that, although Dr. [ ] signed Form FDA 1572 for protocol # [ ] you and Dr. [ ] are listed as the clinical investigators on the form. Dr. [ ] left your division prior to the enrollment of any study subjects, and you informed the IRB on March 3, 2005 that you would be the investigator for the study. Therefore, we consider you to be the investigator for study [ ] Your general responsibilities as an investigator (21 CFR 312.60) include ensuring that the clinical trials are conducted according to the signed investigator statements, the investigational plans, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation. When a clinical investigator signs Form FDA 1572, he or she specifically agrees to personally conduct the clinical trials or to supervise those aspects of the trials that he or she did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator, you may not delegate your general responsibilities.

Our investigation indicates 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 statements, the investigational plans, and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects. Your lack of supervision led to the observations discussed below.

4. **You failed to assure that an IRB that complies with the requirements set forth in Part 56 was responsible for the initial and continuing review and approval of the proposed clinical study, and you failed to assure that all changes in the research activity were promptly reported to the IRB and that changes to the research received IRB approval [21 CFR 312.66].**

   a. Our investigation revealed that changes to the #[ ]protocol were implemented without IRB approval. During the inspection, the FDA investigator learned that copies of all IRB documents pertaining to this study were not maintained at your site. A review of the IRB's file for this study revealed two protocol submissions from your site. The first submission was received by the IRB on 3/8/04. In the version of the protocol received by the IRB on 3/8/04, the inclusion criteria stated that subjects would be 3 months post cardiac transplant and that there would be two groups of diabetic patients eligible within this population: 1) those who were diabetic before transplantation would be automatically eligible; and 2) subjects who are found to have one fasting morning blood sugar more than 100 mmol/dL would be requested to have further testing for diabetes by doing a 75 gm oral glucose tolerance test, and if their blood sugar is more than 200 mmol/dL after 2 hours, they would be eligible to enter the study as a diabetic.

   The second submission was received by the IRB on 2/9/07 after all subjects had been enrolled (initial subjects consented on 8/3/06; last subject consented on 1/11/07). Although it appears that the purpose of this submission was to remove [ ] name from the research, this version of the protocol also has different inclusion criteria. This version of the protocol stated that subjects would be 2-6 weeks post-cardiac transplant. It further stated that patients who were diabetic before transplantation would be eligible if their treatment did not involve insulin or more than 2 oral hypoglycemic agents. Patients who are identified as having fasting blood glucoses of more than 126 or random blood glucose of more than 200 on one occasion would be eligible if their OGTT value exceeded 200. The IRB re-approved the study on 3/7/07; however, during the FDA inspection of the IRB, it was confirmed that the IRB was unaware of modifications to the protocol because you did not follow the IRB's procedures for submitting modifications to previously approved research.

   Due to poor recordkeeping, the FDA investigator had difficulty making a determination regarding which version of the protocol was operational during the study. A review of study records revealed 4 copies of the protocol at your site labeled "Version 1", "Version 2", "Version 3", and "Version 4". Both you and Dr. [ ](who assumed investigator responsibilities in March 2007), stated "Version 4" was the version used during the study. Inclusion criteria in

Version 4 stated that patients would be two weeks post cardiac transplant with impaired glucose tolerance, that is a fasting blood glucose of more than or equal to 100-125 mg/dl on 2 or more occasions, as well as frank diabetics with fasting blood glucose of more than 126 mg/dl on 2 occasions or more. Our investigation failed to confirm that "Version 4" of the protocol ever received IRB review and approval.

b. Our investigation revealed that IRB approval for the study expired on 12/14/06. Three subjects (8, 9, and 10) were consented for the study in January 2007. On 2/23/07, the IRB suspended the research study and requested information from you. The IRB did not re-approve the research study until 3/7/07; therefore, these subjects were enrolled during the time-period when IRB approval had expired.

5. You failed to conduct the study according to the investigational plan [21 CFR 312.60].

The version of protocol [ ] approved by the IRB on 11/17/04 required the following:

a. The protocol required that patients placed on rosiglitazone would start at a dose of 4 mg/day and titrate up to 8 mg/day over 6 weeks. Subject 3 underwent cardiac transplant on 6/17/06 and was enrolled in the study on 8/3/06. The subject was started on 2 mg/day and was titrated up to 6 mg/day 3 months later in November 2006. Subject 5 underwent cardiac transplant on 8/23/06 and was enrolled in the study on 9/7/06. The subject was on 4 mg/day of rosiglitazone throughout the study.

b. For the first 6 weeks after initiation of rosiglitazone, the protocol required weekly phone calls to assess variations in the subject's weight during the past week. There was no documentation that this protocol requirement was performed for the subjects on rosiglitazone. In your written response, you state that because of frequent in-person clinic visits by the study subjects, these phone calls were not made. We do not accept your response and consider the fact that these phone calls were not made to be a protocol violation.

c. The protocol stated that the study agent rosiglitazone, will be provided to the patient for free by [ ] and subjects signed consent forms that stated rosiglitazone will be provided at no cost. Our investigation revealed that study drug shipped by [ ] to the UCLA pharmacy for use in this study was not used and that subjects were provided with prescriptions for rosiglitazone. Therefore, it does not appear that rosiglitazone was provided at no cost to study subjects.

d. Protocol [ ] required that subjects be randomized to 1.2 mg or 1.8 mg of [ ] or placebo. Subject 381010 was randomized to the 1.2 mg dose of [ ] or placebo. At visit 6, the subject's dose was incorrectly increased to the 1.8 mg dose.

6. **You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].**

   As stated under item 4 above, for protocol [ ] subjects were provided with prescriptions for rosiglitazone rather than given the study drug provided by [ ] and no drug accountability records were maintained. In your written response, you admitted that the investigators did not xerox the prescriptions and did not count the pills and that there was no "real time" accounting for the use of rosiglitazone. In addition, our investigation failed to reveal that there was any documentation to show that the patients filled their prescriptions. Therefore, our investigation was unable to verify that study subjects received the appropriate study drug in the dosage specified by the protocol.

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

   a. In seeking informed consent, the information provided to each subject must include a description of the procedures to be followed [21 CFR 50.25(a)(1)]. For protocol [ ] the description of the procedures to be followed that are contained in the consent form are inaccurate in that subjects were told that if they participate in the study, they will either be on the drug rosiglitazone or on a placebo. Our investigation revealed that a placebo was not used in the study.

   b. The consent form did not note the possibility that the Food and Drug Administration may inspect the records, as required by 21 CFR 50.25(a)(5).

   c. 21 CFR 50.20 requires that the information that is given to the subject or the representative shall be in language understandable to the subject or the representative. Informed consent also must be documented by the use of the written consent form approved by the IRB and signed and dated by the subject at the time of consent [21 CFR 50.27(a)]. FDA regulations provide two mechanisms by which subjects may be provided informed consent. Investigators may use a written consent document that embodies the elements of informed consent required by 21 CFR 50.25 [21 CFR 50.27(b)(1)]. Alternatively, investigators may use a short form written consent document stating that the elements of informed consent required by § 50.25 have been presented orally. When the short form written consent is used, there shall be a witness to the oral presentation and the IRB shall approve a written summary of what is to be said. The subject (or the subject's representative) must sign the short form. The witness must sign the short form and the summary. Finally, copies of the summary and short form shall be given to the subject or representative [21 CFR 50.27(b)(2)]. For protocol [ ] all enrolled subjects spoke Spanish as their primary language, yet they originally signed English language consent forms. Although you stated in your response letter that the subjects were orally provided informed consent in Spanish, you did not provide information to show that all of the requirements of 21 CFR 50.27(b)(2) were met.

After Dr.[ ]assumed investigator responsibilities in April 2007, the subjects were re-consented with Spanish language consent forms.

8. **You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].**

   a. For protocol[ ]there was no documentation that subjects had been treated with one or more oral anti-diabetic drugs for at least 3 months before screening as required by the protocol. We note that there were no medical histories in these subjects' research files. For subjects 381001, 381003, 381007, 381009, and 381010, you created Memos to File stating that medical records were not obtained due to subjects' primary care physicians being located in Mexico. These memos do not sufficiently address the issue of the missing medical histories. Without the medical histories, i.e., history of taking an oral anti-diabetic drug, it is not possible to verify if the subjects met inclusion criteria for the study.

   b. For protocol[ ]EKG printouts are imprinted with incorrect dates that are off by decades and into the future in most cases. On some printouts the dates are corrected, and on others the dates are not corrected.

      - For subject 381001, the EKG is imprinted with the date of Jan. 19, 2038, which has been crossed out and changed to Dec. 11, 2006.
      - For subject 381003, the EKG is imprinted with the date of Oct. 18, 2033.
      - For subject 381004, the EKG is imprinted with the date of Oct. 18, 2033, which has been crossed out and changed to Jan. 16, 2007.
      - For subject 381006, the EKG is imprinted with the date of Oct 18, 2033, which has been crossed out and changed to Dec. 13, 2006.
      - For subject 381007, the EKG is imprinted with the date of Oct. 18, 2033.
      - For subject 381010, the EKG is imprinted with the date of Jan. 1, 1970.
      - For subject 381011, the EKG is imprinted with the date of Jan. 1, 1970, which has been crossed out and changed to Oct. 20, 2006.

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 that the corrective actions outlined in your written response have been implemented. 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 (301) 796-3397; FAX (301) 847-8748. 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
Division of Scientific Investigations, Bldg. 51, Room 5354
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
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 K BALL
05/30/2008