



WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Hollis J.C. Underwood, M.D.
Sonoran Health Specialists, Inc.
8414 East Shea Boulevard, Suite 103
Scottsdale, Arizona 85260

Ref: 07-HFD-45-0101

Dear Dr. Underwood:

Between April 26 and May 10, 2006, Dr. Sandra L. Shire, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of a clinical investigation (protocol [] entitled: [] of the investigational drug [] performed for []

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 of the study have been protected.

We are aware that at the conclusion of the inspection, Dr. Shire presented and discussed with you Form FDA 483, Inspectional Observations.

From our review of the establishment inspection report and the documents submitted with that report, 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 acknowledge receipt of your written response to Form FDA 483, dated June 16, 2006, and wish to emphasize the following:

- 1. **You failed to personally conduct or adequately supervise the above-referenced clinical trial [21 CFR 312.60].**

When you signed the investigator statement (Form FDA 1572) for the above-referenced clinical trial, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities (21 CFR 312.60) included ensuring that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations and in a manner that protects the rights, safety, and welfare of subjects under your care. You specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial

that you 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 trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects.

You delegated responsibilities to a site management organization (SMO), [] The CEO of [] Mr. [] functioned as one of the study coordinators for the clinical trial. It appears that Mr. [] conducted the clinical trial without any supervision by you, which resulted in the following:

- Enrollment of subjects who did not meet inclusion/exclusion criteria.
- Unqualified personnel performing study procedures; specifically, [] who is a pharmacist, was performing physical exams.
- Falsification of your signature on study documents.
- Unknown signatures on study documents.
- Inaccurate study records; specifically, information in source documents did not match information in case report forms (CRFs).

We note that prior to the inspection of the [] study, an FDA inspection was conducted at your site in February 2005. This inspection was initiated based on correspondence from [] that due to your lack of supervision, protocol [] was terminated at your site. The same SMO [] and study coordinator [] worked on the [] study.

It appears that the FDA inspection in February 2005 did not prompt you to review research practices at your site and implement corrective actions, until the problems with the [] study were brought to your attention in September 2005.

2. You failed to protect the rights, safety, and welfare of subjects under your care [21 CFR 312.60].

- a) The protocol required a physical exam (including a cardiovascular physical exam) at the screening visit. The cardiovascular physical exam consisted of the following assessments: heart (jugular venous distension), left ventricular gallop (S3), carotid bruits, femoral/abdominal bruits, rales on pulmonary auscultation, atrial fibrillation, presence of peripheral edema and an assessment of the edema as mild or marked, and presence of angina and an assessment of the angina as stable, yes or no.

According to the Signature Sheet/Delegation of Responsibility Log, only you and sub-investigators, [] M.D., and [] M.D. had the responsibility to perform subject evaluations.

Our investigation has determined that in at least 6 cases an unqualified person (lacking medical credentials) performed the physical exams required by the protocol.

- In one case, [] performed the physical exam and cardiovascular physical exam.
 - In two cases, [] performed the physical exam.
 - In one case, [] or the study nurse performed the physical exam.
 - One subject never saw any physicians.
 - In one case, the nurse performed the physical exam.
- b) The protocol required clinical labs (CBC, chemistries, HbA1c, lipid profile, CRP, serum pregnancy test, and urinalysis) at the screening visit. The protocol required that investigators review the labs upon receipt and make a determination of clinical significance for labs outside the normal range. All laboratory reports must be reviewed and signed by a medically trained investigator.
- For the following subjects, the signature on the lab reports does not match any of the physician signatures that are documented on the Signature Sheet/Delegation of Responsibility Log; therefore, it is not known if these lab reports were ever reviewed by you, or a qualified sub-investigator, prior to enrolling these subjects in the clinical trial.
- Subject 3711, screening apolipoproteins, chemistry panel, HbA1c, CRP, lipids, CBC, urinalysis, and urine chemistry.
 - Subject 3712, screening apolipoproteins, chemistry panel, HbA1c, CRP, lipids, CBC, urinalysis, and urine chemistry.
- c) The protocol required an ECG at the screening and randomization visits. The protocol required that investigators initial and date the ECG reports upon receipt. Further, if the investigator's interpretation of any protocol-specified or unscheduled ECG differs from that supplied by central ECG laboratory, it is the responsibility of the investigator to make the final clinical decisions.

For subject 3711, the signature on the screening and randomization ECG tracings does not match any of the physician signatures that are documented on the Signature Sheet/Delegation of Responsibility Log; therefore, it is not known if these ECGs were ever reviewed by you, or a qualified sub-investigator, prior to enrolling this subject in the clinical trial.

3. You failed to conduct the study according to the approved protocol [21 CFR 312.60].

a) Protocol inclusion criterion #3 required male or female subjects in one of the two following groups:

- Subjects with diabetes mellitus (NIDDM or IDDM) 18 years of age or older
- Subjects (without diabetes mellitus) 55 years of age or older with one of the following additional risk factors:

(1) Age 60 or older

(2) Low HDL-C as evidenced by:

(i) Male: HDL-C < 40 mg/dL for US subjects

(ii) Female: HDL-C < 50 mg/dL for US subjects

(3) Previous Myocardial Infarction (in addition to the index event in Inclusion Criteria 2a), or diagnosis of atherosclerosis in a non-coronary vessel (e.g. history of prior stroke, presence of PVD)

(4) Prior history of CHF or ejection fraction < 40%

Subject 3476 (male), age 58 (DOB, [] at screening on 8/19/04 did not have one of the additional risk factors as noted above and should not have been enrolled in the study. HDL-C at screening was 48 mg/dL. The CRF was incorrectly marked that the HDL-C was < 40 mg/dL.

b) The protocol requires a physical exam (including a cardiovascular physical exam) and a New York Heart Association Classification at the screening visit. Subject 5000 did not have these protocol-required procedures performed at the screening visit.

4. You failed to prepare and 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)].

In your affidavit, dated April 26, 2006, you state that “On or about September 2005, I became aware of problems with the conduct of the study, specifically, that Mr. [] forged my signature on numerous documents, including Case Report Forms (CRFs), a letter requesting additional money from the sponsor, and lab reports.” You also state that the signature on Form FDA 1572, “dated 9-8-04 is a forged signature and I had never seen it before today.”

a) The following documents are signed with an unknown or possibly forged signature; had you been supervising the clinical trial, as you committed to do when you signed Form FDA 1572, these signatures would have been apparent to you.

i. Subject 3476

- Source document: physical exam, cardiovascular physical exam, and New York Congestive Heart Failure Classification

ii. Subject 3711

- Source document: physical exam, cardiovascular physical exam, and New York Congestive Heart Failure Classification
- CRF signature page confirming information in the CRF is accurate
- Screening and randomization ECGs
- Screening lab reports

iii. Subject 3712

- Screening lab reports
- CRF signature page confirming information in the CRF for visit M03 is accurate

iv. Subject 4196

- Source document: cardiovascular physical exam and New York Congestive Heart Failure Classification

b) For subject 3476, the CRF for the screening visit is marked “Yes” to the statement: “HDL-C < 40 mg/dL for US Subjects or < 1.0 mmol/L for non-US Subjects”. The screening lab report, dated 8/20/04, documented an HDL-C of 48 mg/dL.

c) For subject 4193, the CRF for visit M03 on 1/18/05, is marked that no clinical study end points occurred since the subject’s last visit. The source document is marked that the subject experienced a stroke or transient ischemic attack since the last visit. Stroke and transient ischemic attack are clinical study end points.

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. We have reviewed your written response to Form FDA 483, dated June 16, 2006, and acknowledge the corrective actions described in the response. We understand that you are no longer the clinical investigator for the clinical trial and that investigator responsibilities have been assumed by [] M.D.

Your written response, however, does not negate the fact that when you were the clinical investigator for the clinical trial you did not supervise the investigation.

Within fifteen (15) working days of your receipt of this letter, you must notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. 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) 827-7279, FAX (301) 827-5290. 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, HFD-46
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Gary J. Della'Zanna, D.O., MSc.
Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Gary DellaZanna
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