



WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Reference No. 06-HFD-45-0801

Professor Olga D. Ostroumova
Department of Internal Medicine #3
Moscow City Hospital #23
11 Yauzskaya Str.
109240 Moscow, Russia

Dear Professor Ostroumova:

Between February 15 and February 17, 2006, Ms. Linda R. Kuchenthal and Dr. Mathew Thomas, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigation:

Protocol [] entitled "A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Assess the Clinical Benefit of Midodrine Hydrochloride in Patients with Neurogenic Orthostatic Hypotension" of the investigational drug midodrine hydrochloride (ProAmantine), performed for Shire Pharmaceutical Development, Inc.

We understand that this study was conducted under a U.S. Investigational New Drug Application (IND) and thus, is subject to the U.S. Code of Federal Regulations (CFR). Therefore, we are providing comments so that you will be aware of FDA's requirements for clinical studies conducted under U.S. IND.

Based on our evaluation of the establishment inspection report, the documents and information obtained in the course of the inspection, your written response dated March 22, 2006, and the Form FDA 483, Inspectional Observations, we conclude that you violated the regulations governing the proper conduct of clinical studies involving investigational new drugs, at 21 CFR Part 312. The applicable sections of the CFR are cited for the violations listed below.

1. You failed to maintain adequate and accurate case histories that record all observations and data pertinent to the investigation [21 CFR 312.62(b)].

Specifically, the investigation found:

- a. For Subject #66-01, the baseline ECG recording obtained on June 21, 2004, and the Visit 4 ECG recording obtained on August 3, 2004, were identical except for the information hand-written on each ECG, including subject number and date of tracing.
- b. For Subject #66-03 the baseline ECG recording obtained on June 21, 2004, and the Visit 4 ECG recording obtained on Aug 2, 2004, were identical except for the information hand-written on each ECG, including subject number and date of tracing.

In your response letter of March 22, 2006, you stated that both subjects requested copies of their Visit 1 ECGs and that copies were made but which were stored with the study record instead of being given to the subjects but then at Visit 4, these same subjects were mistakenly given copies of their Visit 4 ECGs instead of their Visit 1 ECGs. Your explanation does not adequately explain why each subject had identical ECGs at Visit 1 and Visit 4 that were hand dated with different dates.

- c. Source records for Subjects #66-01 and #66-02 document that the same individual [] performed the baseline physical examinations on the same day (June 21, 2004) and at the same time (0900).
- d. Source records for Subject #66-04 indicate that sub-investigator [] recorded the Visit 3E blood pressure on July 20, 2004 at 9AM while personally evaluating and recording Visit 3E blood pressure for Subject #66-05 at the same time and date.
- e. Source records for Subject #66-04 indicated that sub-investigator [] recorded the Visit 4 source notes on at 0800 on August 2, 2004 while recording the Visit 4 source notes for Subject #66-03 at the same time and date.

During the inspection you reported to FDA that records were recorded contemporaneously while subjects were evaluated. In your letter of March 22, 2006, you explained that the two subjects had measurements performed at the same time by two different investigators, at different compartments of the hospital. Your explanation does not adequately explain how one sub-investigator could perform procedures and measurements on one patient while simultaneously evaluating and writing notes in the medical chart for another patient. Furthermore, the protocol specified that the blood pressure device must be calibrated and

approved in writing by a Shire or [] representative. During the inspection and the FDA 483 discussion, you did not inform the FDA investigators that you were using two different devices. We also note that you have not provided documentation to support your claim that the two instruments used for measuring blood pressure were certified.

- f. For Subject #66-01, Visit 6 on August 31, 2004, there were two different source records contained in the study chart.

In your letter you stated that you asked the sub-investigator to re-write the source notes with fewer corrections. However, source records should record information contemporaneous to the study visit, and should not be rewritten.

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

Specifically, the investigation found source notes for Subject #66-05 showing that for Visit 3A on July 2, 2004, 100 x 5 mg tablets of study drug were dispensed by [] but that 86 x 2.5 mg tablets were returned at Visit 3B on July 9, 2004 to sub-investigator []. The study drug accountability record for Subject #66-05 shows that sub-investigator [] dispensed 100 x 5 mg tablets on July 2, 2004. This record was changed on August 13, 2004, to reflect that 100 x 2.5 mg tablets were dispensed. The study records do not account for this discrepancy.

In your letter you acknowledged the discrepancy in the study drug accountability record, and that the error was corrected after the study monitor detected it.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational products. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

Within fifteen (15) days of 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.

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If you have questions, please contact Leslie Ball, M.D. at (301) 594-1032, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place,
Rockville, Maryland 20855

Sincerely yours,

Joseph P. Salewski
Director (Acting)
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
this page is the manifestation of the electronic signature.**

/s/

Joseph Salewski
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