



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**WARNING LETTER**

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Richard A. Wright, M.D.  
550 S. Jackson Street  
3<sup>rd</sup> Floor ACB  
Louisville, KY 40202-1622

Ref: 09-HFD-45-02-01

Dear Dr. Wright:

Between April 29 and May 28, 2008, Ms. Lauren Collins, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation [protocol (b) (4) entitled "A Phase 3 Study to Evaluate the Efficacy and Safety of (b) (4) and an Active Comparator, Lansoprazole (30 mg QD) on Healing of Erosive Esophagitis"] of the investigational drug (b) (4), performed for (b) (4).

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 those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your June 2, 2008 letter written in response to the Form FDA 483, Inspectional Observations, 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. Collins presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

**1. You failed to conduct the studies, or ensure they were conducted, according to the investigational plan [21 CFR 312.60].**

- a. Of sixteen subjects enrolled in the study, ten subjects had biopsies taken during the screening endoscopy in contravention of the protocol. Administrative change letter #1, dated February 16, 2006, was approved by the Institutional Review Board (IRB) on April 10, 2006. The letter states that "gastric biopsies will only be taken if the subject has a maintenance of healing study available at the site." However, your study site did not have a maintenance of healing study. Therefore, the following subjects had biopsies taken after April 10, 2006, in violation of the protocol:

- i. Subject (b) (6): biopsy performed on April 13, 2006
- ii. Subject (b) (6): biopsy performed on April 14, 2006
- iii. Subject (b) (6): biopsy performed on April 14, 2006
- iv. Subject (b) (6): biopsy performed on April 26, 2006
- v. Subject (b) (6): biopsy performed on May 8, 2006
- vi. Subject (b) (6): biopsy performed on May 10, 2006
- vii. Subject (b) (6): biopsy performed on May 8, 2006
- viii. Subject (b) (6): biopsy performed on May 18, 2006
- ix. Subject (b) (6): biopsy performed on May 31, 2006
- x. Subject (b) (6): biopsy performed on June 15, 2006

- b. Of sixteen subjects enrolled in the study, seven subjects had a CLO test (Campylobacter-Like Organism test), which involved a biopsy, performed during screening endoscopy, in violation of the protocol. Administrative change letter #1, dated February 16, 2006, was approved by the IRB on April 10, 2006. The letter states that "a definitive CLO test will only be performed for those subjects who test positive for *H. pylori* by finger stick or serology at screening and have erosive esophagitis (EE)." CLO tests were performed for the following subjects who had a negative serology or finger stick test for *H. pylori* after April 10, 2006, in violation of the protocol:

- i. Subject (b) (6): CLO test performed on April 13, 2006
- ii. Subject (b) (6): CLO test performed on April 26, 2006
- iii. Subject (b) (6): CLO test performed on May 10, 2006
- iv. Subject (b) (6): CLO test performed on May 8, 2006
- v. Subject (b) (6): CLO test performed on May 19, 2006
- vi. Subject (b) (6): CLO test performed on May 31, 2006
- vii. Subject (b) (6): CLO test performed on May 31, 2006

c. As specified in the protocol, subjects with abnormal laboratory values were to be excluded from the study. For five of sixteen enrolled subjects, you did not review the screening laboratory results until after the subjects were enrolled in the treatment phase of the study. Because subjects with abnormal laboratory values were to be excluded, the protocol required you to review subjects' lab results prior to their enrollment in the treatment phase. The details for these subjects are provided below.

i. Subject (b) (6) screening labs were collected on April 27, 2006; the Day -1 visit was conducted on May 10, 2006. The screening labs were not reviewed until May 12, 2006, after the subject was enrolled in the treatment phase of the study.

ii. Subject (b) (6) screening labs were collected on May 1, 2006; the Day -1 visit was conducted on May 11, 2006. The screening labs were not reviewed until June 5, 2006, after the subject was enrolled in the treatment phase of the study.

iii. Subject (b) (6) screening labs were collected on May 1, 2006; the Day -1 visit was conducted on May 9, 2006. The screening labs were not reviewed until June 5, 2006, after the subject was enrolled in the treatment phase of the study.

iv. Subject (b) (6) screening labs were collected on May 9, 2006; the Day -1 visit was conducted on May 19, 2006. The screening labs were not reviewed until June 5, 2006, after the subject was enrolled in the treatment phase of the study.

v. Subject (b) (6) screening labs were collected on May 15, 2006; the Day -1 visit was conducted on June 2, 2006. The screening labs were not reviewed until June 5, 2006, after the subject was enrolled in the treatment phase of the study.

d. The protocol states that a complete physical exam will be performed at the Week 4 visit. For fourteen of sixteen enrolled subjects, however, the Week 4 exam worksheets document only brief physical exam results. Brief exam results at Week 4 were documented for Subjects (b) (6).

In your June 2, 2008 response to the Form FDA 483 you stated that you have implemented a "Compliance Checklist" to avoid these errors. We acknowledge your assurance that corrective actions have been taken prevent similar findings from occurring in any future studies.

e. The inclusion criteria of the protocol states that subjects must "agree to continued use of a double barrier method of birth control." However, a double barrier method of birth control was not documented for Subjects (b) (6), who were all female subjects of childbearing potential.

**2. You failed to promptly report all changes in research activity to the IRB [21 CFR 312.66].**

You did not promptly report all changes in research activity to the IRB, as required by the regulations and the protocol. Specifically, on June 26, 2006, all screening activity at your site was stopped until noncompliance issues were corrected. However, you did not notify the IRB that the study was closed to enrollment until you submitted a continuing review report in November 2006.

In your June 2, 2008 response to the Form FDA 483 you stated that you have implemented a “Compliance Checklist” to avoid these errors. We acknowledge your assurance that corrective actions have been taken prevent similar findings from occurring in any future studies.

**3. You failed to properly document informed consent by the use of a written informed consent form approved by the IRB [21 CFR 50.27(a)].**

Of sixteen subjects enrolled in the study, seven subjects signed an outdated screening informed consent form (ICF). On April 25, 2006, the IRB approved a new (April 14, 2006) version of your ICF. However, in May and June of 2006, subjects in your study were given an outdated version of the ICF (which was drafted on March 24, 2006 and approved by the IRB on April 5, 2006). Specifically:

- a. Subject (b) signed the March 24, 2006 version of the ICF on May 5, 2006.
- b. Subject (b) signed the March 24, 2006 version of the ICF on May 9, 2006.
- c. Subject (b) signed the March 24, 2006 version of the ICF on May 9, 2006.
- d. Subject (b) signed the March 24, 2006 version of the ICF on May 15, 2006.
- e. Subject (b) (6) legally authorized representative signed the March 24, 2006 version of the ICF on May 15, 2006.
- f. Subject (b) signed the March 24, 2006 version of the ICF on May 19, 2006.
- g. Subject (b) signed the March 24, 2006 version of the ICF on June 6, 2006.

In your June 2, 2008 response to the Form FDA 483 you stated that you have implemented a “Compliance Checklist” to avoid these errors. We acknowledge your assurance that corrective actions have been taken prevent similar findings from occurring in any future studies.

**4. You failed to ensure that the investigation was conducted according to the signed investigator statement (Form FDA-1572) [21 CFR 312.60].**

Specifically, study procedures were conducted by personnel not yet listed on the Form FDA-1572, Statement of Investigator. When you signed the investigator statement for the above referenced clinical investigation, you agreed to take on the responsibilities of a clinical investigator at your site. The responsibilities of a clinical investigator include allowing only personnel listed on the 1572 to perform study procedures. By allowing the following procedures to be performed by

subinvestigators who were not yet listed on the Form FDA-1572, you failed to comply with the general responsibilities of a clinical investigator as stated in 21 CFR 312.60. For example, the following procedures were performed by a physician or physician assistant (PA) not listed on the Form FDA-1572 at the time the procedures were performed.

- a. Two screening endoscopies for Subjects (b) (6) were performed on May 18, 2006. The investigator was not added to the Form FDA-1572 until August 1, 2006.
- b. Nine screening physical exams for Subject (b) (6) and were performed between March 29, 2006 and May 19, 2006. The investigators were not added to the Form FDA-1572 until June 20, 2006.
- c. Twelve Day -1 physical exams for Subject (b) (6) were performed between April 14, 2006 and June 12, 2006. The investigators were not added to the Form FDA-1572 until June 20, 2006.
- d. One GERD Symptom Assessment at screening for Subject (b) (6) was performed on May 1, 2006. The investigator was not added to the Form FDA-1572 until June 20, 2006.
- e. Three Week 4 endoscopies for Subjects (b) (6) were performed between May 22, 2006 and July 3, 2006. The investigator was not added to the Form FDA-1572 until August 1, 2006.
- f. Eight Week 4 physical exams for Subjects (b) (6) were performed between May 11, 2006 and July 3, 2006. The investigators were not added to the Form FDA-1572 until June 20, 2006.

In your June 2, 2008 response to the Form FDA 483 you stated that you have implemented a "Compliance Checklist" to avoid these errors. We acknowledge your assurance that corrective actions have been taken prevent similar findings from occurring in any future studies.

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 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 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:

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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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LESLIE K BALL  
02/18/2009