DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 06-HFD-45-1201

Robert Michael Murray, MD
Capstone Clinical Trials, Inc.
3106 Independence Drive,
Homewood, AL 35209

Dear Dr. Murray:

Between September 11 and 14, 2006, Investigators Dana M. Daigle and Barbara D. Wright of the Food and Drug Administration (FDA), conducted an investigation and met with you and your staff to review your conduct of a clinical investigation Protocol [ ]"Prospective, randomized, double-blind, three-armed, multi-center comparative trial to evaluate the efficacy of[ ]300 mg PO, BID for 7 days versus [ ]300 mg PO, BID for 10 days versus cefuroxime axetil 250 mg PO BID for 10 days in the treatment of acute bacterial sinusitis", 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 those studies have been protected.

We are aware that at the conclusion of the inspection, the FDA investigators presented and discussed with you Form FDA 483, Inspectional Observations; and have reviewed your response to the matters discussed in the Form FDA 483, dated October 16, 2006 that you submitted to Ms. Carol Sanchez, Acting Director, FDA - New Orleans District.

From our review of the establishment inspection report, the documents submitted with that report, and your response dated October 16, 2006, 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 wish to emphasize the following:

1. **FAILURE TO PERSONALLY CONDUCT OR SUPERVISE THE CLINICAL INVESTIGATION [21 CFR 312.60]**

   When you signed the investigator statements (Form FDA 1572) for the above referenced clinical investigation, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities (21 CFR 312.60) include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations protecting the rights, safety and welfare of subjects participating in the investigation. You specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals or firms qualified to perform such tasks, as 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 clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, in a manner that protected the rights, safety, and welfare of human subjects.

   Specifically, during the FDA inspection you informed the FDA investigators that you did not personally meet with at least two sub-investigators (Drs. [ ] and [ ] who conducted the study, nor reviewed their research or clinic records regarding the subjects they enrolled. You also informed FDA investigators that you were not aware that all the screening x-rays obtained by the two sub-investigators were re-interpreted by a second radiologist at the end of the study and that you were also not aware that only the results from the second radiologist were reported to the sponsor. You also stated that you did not review the inclusion criteria, treatment outcomes, protocol deviations, or adverse event documentation for the subjects enrolled by these sub-investigators.

   The protocol violations listed below may have also resulted, at least in part, from a lack of your direct involvement in the conduct of the study or your lack of personal supervision of personnel involved in assisting you with the conduct of those studies.

2. **FAILURE TO FOLLOW INVESTIGATIONAL PLAN [21 CFR 312.60].**

   Specifically,

   a. The Inclusion Criteria section of the protocol included that subjects should have a clinical diagnosis of acute sinusitis with signs and symptoms >7 days but <28 days, as defined by the presence of 1 or more of the following on a radiographic paranasal sinus film (Waters view):
      i. evidence of air-fluid levels
      ii. opacification
      iii. ≥6 mm mucosal thickening

The Criteria for Trial Objectives and Safety Evaluation section of the protocol included that "acute sinusitis must have been diagnosed at enrollment by the inclusion and exclusion criteria and confirmed by a radiologist's written report of the sinus x-ray."

The Enrollment Procedures section of the protocol specified that "a Waters' view x-ray will be obtained. While the patient may be enrolled if in the clinical investigator's clinic judgment the radiographic findings are consistent with the inclusion criteria, the radiologist's written report will be used to determine the patient's validity. This written report must be included in the source documents."

The protocol did not specify that x-rays films could be re-read by a second radiologist if one radiologist's evaluation of the sinus x-rays determined that a subject did not meet the inclusion criteria specified in the protocol, or if the clinical investigator disagreed with a radiologist's evaluation of the sinus x-ray interpretation.

For the following study subjects, the pre-therapy x-rays were re-interpreted by a second radiologist after enrollment and completion of study-related procedures to indicate that they qualified for study inclusion. The initial radiologist's evaluation determined that these subjects did not meet the radiographic inclusion criteria:

i. Subject 47039 had a pre-therapy x-ray on August 23, 2001, which was evaluated as "normal" by a radiologist. The subject was enrolled on August 23, 2001 and completed the study on September 24, 2001, but on October 26, 2001 a second radiologist was engaged to re-interpret the x-ray. The re-interpretation indicated an abnormal finding of mucoperiosteal thickening $\geq$ 6mm in both the left and right sinus.

ii. Subject 47040 had a pre-therapy x-ray on August 28, 2001, which was evaluated by a radiologist and showed a retention cyst in the right maxillary sinus. The x-ray report did not record any of the findings of sinusitis specified by the protocol for enrollment. The subject was enrolled on August 28, 2001 and the last visit was on October 12, 2001, but on October 26, 2001 a second radiologist was engaged to re-interpret the x-ray. The re-interpretation indicated a finding of right mucoperiosteal thickening $\geq$ 6 mm.

iii. Subject 47045 had a pre-therapy x-ray on September 17, 2001, which was evaluated as "normal" by a radiologist. The subject was enrolled on September 17, 2001, and completed the study on October 17, 2001, but on October 26, 2001 a second radiologist was engaged to re-interpret the x-ray. The re-interpretation indicated a finding of mucoperiosteal thickening $\geq$ 6mm in the right sinus.

b. Subject 47046 was not eligible for study enrollment because of a history of 10 sinus infections and 3 surgical procedures for sinus difficulties, documenting that the subject had chronic sinusitis, a criterion for study exclusion.

c. Subject #47030 was treated with prednisone, a systemic corticosteroid which was contraindicated during the study.

d. Subject #47048 was administered Nasacort AQ, a corticosteroid which was contraindicated during the course of the subject's therapy including the post-treatment follow-up period.

e. While assigning subjects to study treatment, our investigation found that you skipped the randomization number 1533 twice, thereby violating the protocol specified randomization plan of not missing or substituting any numbers. This protocol deviation involved the randomization of subjects #47045, 47046 and 47047.

3. **FAILURE TO PREPARE AND MAINTAIN ADEQUATE AND ACCURATE CASE HISTORIES [21 CFR 312.62 (b)].**

   Specifically, the baseline and test-of-cure x-ray films for 2 subjects (47041 and 47050) were not available for inspection.

4. **FAILURE TO PROMPTLY REPORT TO THE SPONSOR AN ADVERSE EFFECT THAT MAY REASONABLY BE REGARDED AS CAUSED BY, OR PROBABLY CAUSED BY, THE DRUG. [21 CFR 312.64 (b)].**

   Specifically, the pulsatile tinnitus experienced by subject #47039 was not reported on the subject's case report form and was not reported to the sponsor.

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. Include any documentation necessary to show that corrections have been achieved. 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 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
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

*{See appended electronic signature page}*

Gary Della'Zanna, D.O., M.Sc
Director
Division of Scientific Investigations, HFD-45
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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Gary DellaZanna
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