DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

# WARNING LETTER

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

Nagarjuna R. Ponugoti, M.D.
Allergy, Asthma & Immunology
Associates of Terre Haute
4779 S. 7th Street
Terre Haute, Indiana 47802

Ref: 08-HFD-45-0202

Dear Dr. Ponugoti:

Between September 10, 2007 and September 19, 2007, Ms. Kimberly Martin, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol [ ] entitled, "An Epidemiologic Study of [ ] Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma [ ]" 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.

From our review of the establishment inspection report, the documents submitted with that report and your September 27, 2007, 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.

We are aware that at the conclusion of the inspection, Ms. [ ] presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to obtain and adequately document informed consent in accordance with 21 CFR 50 [21 CFR 312.60].**

   Informed consent must be documented by the use of a written consent form approved by an Institutional Review Board (IRB) and signed and dated by the subject or the subject's legally authorized representative at the time of consent [21 CFR 50.27, see 21 CFR 312.60]. As an investigator, it is your responsibility to obtain informed consent in a written consent form approved by an IRB in compliance with the requirements of 21 CFR Part 50 [see 21 CFR 312.60]. Except as provided in 21 CFR 50.23 and 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative [21 CFR 50.20]. Our investigation found that for 30 of the 34 subjects enrolled, informed consent was not obtained or documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The IRB approved consent forms were not completed until six months after the start of the study. In addition, assent was not obtained from subjects 46535, 46517, and 46529.

   In your September 27, 2007, written response, you explained that the sponsor did not send the consent form in the starter packages for the study, thus you had subjects sign an "Authorization Form" at the time of enrollment, which provided authorization to use and disclose health information. We find your explanation inadequate. Our review of the authorization form reveals that the form does not contain any of the elements required to be provided to subjects to constitute informed consent as described in 21 CFR 50.25. When you signed the "Statement of Investigator", Form FDA 1572, you agreed to fulfill the responsibilities of a clinical investigator that include ensuring that the requirements relating to informed consent are met. In addition, the protocol specified that "patients must meet all the of the following inclusion criteria to be eligible for study entry: signed informed consent document (in the case of a minor, consent must be given by the child's parent or legally authorized representative)...". The approval letter dated October 27, 2004, from the [ ]Human Research Review Board documents your role as Principal Investigator with responsibility for the study. The approval letter indicates that the IRB reviewed and approved the Adult Consent Form, Minor Consent Form and Child Assent Form, so you should have been aware that these documents were essential to the conduct of the study. It is your responsibility to ensure compliance with these informed consent requirements.

2. **You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects [21 CFR 312.60 and 312.66].**

   An investigator is responsible for ensuring that the investigation is conducted according to the investigational plan and applicable regulations, including promptly reporting to the IRB all unanticipated problems involving risk to human subjects [21 CFR 312.60 and 312.66]. Our investigation found that Subject 46514 died on[

[ ] Subject 46532 died on [ ] and Subject 46505 was hospitalized; however, there is no documentation indicating that you promptly reported this information to the IRB.

During the inspection, you explained to the FDA investigator that you were unaware that you needed to report serious adverse events to the IRB, although you attended the Investigator's Meeting, read the protocol and signed the investigator's agreement. In your written response you state that you were under the impression that the sponsor would communicate with the IRB. We find your response unacceptable. When you signed the "Statement of Investigator," Form FDA 1572, you agreed to comply with all of the responsibilities of a clinical investigator, including promptly reporting to the IRB all unanticipated problems involving risks to human subjects or others. In addition, the protocol specifically states in section 6.4 that "the Principal Investigator must also keep the IRB informed of any significant adverse events."

3. **You continued to conduct clinical investigation related activities despite the fact that IRB approval had been withdrawn. [21 CFR 312.66, and 56.103(a)].**

FDA regulations require that clinical investigations conducted under an IND (i.e. those subject to 21 CFR Part 312) be reviewed, approved, and under continuing review by an IRB meeting the requirements of 21 CFR Part 56 [see 21 CFR 56.103]). Clinical investigators are responsible for assuring that an IRB conducts initial and continuing review of clinical investigations [21 CFR 312.66]. You violated these requirements by continuing to see and treat study subjects after [ ] Human Research Review Board withdrew approval of your clinical investigation site on May 12, 2005.

Despite your awareness of the withdrawal of IRB approval per the notice you received on May 11, 2005, you continued to obtain informed consent or parental consent from 27 of the 33 subjects previously entered into the study after May 12, 2005. Although [ ] Human Research Board denied the request for you to conduct six-month and twelve-month follow up visits on May 22, 2005, six-month study visits were completed for six study subjects during the period that the clinical investigation was suspended by the IRB. In addition, you pursued obtaining consent from fifteen subjects after you received correspondence withdrawing approval of the clinical investigation.

In your written response, you stated that you did not know you were not permitted to conduct follow up visits after approval had been withdrawn. Your response is inadequate. The IRB correspondence to you clearly documents that approval for the study had been withdrawn, and as the investigator you were responsible for ensuring the continuing approval of the clinical study by the IRB [21 CFR 312.66].

4. **You failed to report to the IRB all changes in the research activity [21 CFR 312.60 and 312.66].**

   Specifically, 21 CFR 312.66 requires clinical investigators to assure that all changes in the research activity are promptly reported to the IRB [see 21 CFR 312.60]. Our investigation found that after having the clinical investigation reinstated by the IRB in September of 2005, you failed to notify the IRB that you were discontinuing the study in February 2006 and failed to submit a final study report. We find your explanation that you thought this was the sponsor's responsibility to be unacceptable. As noted on the Form FDA 1572 that you signed, this responsibility belongs to the clinical investigator and not to the sponsor.

5. **You failed to prepare and maintain adequate and accurate case histories that record all observations and data pertinent to the investigation on each individual [21 CFR 312.62(b)].**

   An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and 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)]. Our investigation found that you did not document the six-month follow-up that was conducted via telephone in the case histories for 22 subjects as required by FDA regulations and the investigation protocol.

As the clinical investigator, you are responsible for ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, applicable regulations, and for protecting the rights, safety and welfare of the study subjects.

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.

If you have any questions, please contact Tejashri Purohit-Sheth, M.D. at (301)796-3402 or FAX (301)847-8748. Your written response and any pertinent documentation should be addressed to:

Tejashri Purohit-Sheth. M.D.
Acting Branch Chief
Good Clinical Practice Branch II, HFD-47

Division of Scientific Investigations, Bldg 51, Room 5358
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, HFD-45
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

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LESLIE K BALL
06/06/2008