DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Jerry M. Herron, M.D.
1207 Rebsamen Park Rd.
Little Rock, AR 72202

Ref: 06-HFD-45-0906

Dear Dr. Herron:

Between May 2 and May 16, 2006, Investigator Mr. Frederic French, of the Food and Drug Administration (FDA New Orleans District Office), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol [ ] titled "A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Clinical Trial Designed to Assess the Safety of Ciclesonide, Applied as a Nasal Spray at Three Dose Levels, 200 µg, 100 µg, or 25 µg Once Daily for Six Weeks, in the Treatment of Perennial Allergic Rhinitis in Pediatric Patients [ ] Years of Age"), of the investigational agent ciclesonide, performed for Altana Pharma.

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 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. The following violations from Statute and IND regulations 21 CFR 312 are noted:

1. **You failed to conduct the study in accordance with the investigational plan [21 CFR 312.60].**

   The protocol specified that certain medications were prohibited at any time during the entire study period, including the screening period, and must not have been used within certain protocol-specified time periods prior to screening. According to the protocol, all antihistamines were to be discontinued at the screening visit and withheld for the entire duration of the study; inhaled corticosteroids were to be discontinued within 30 days of randomization; leukotriene inhibitors were to be

discontinued within 7 days of randomization. Subjects were randomized 7 to 10 days after the initial screening visit. Our investigation found that 7 of 69 subjects were randomized into the study while on prohibited medications. For example:

Subject #	Prohibited Medication	Violation
S50141 R50117 CRF 5109	Singulair chewable	Discontinued 5 days after screening
S50149 R50124 CRF 5116	Benadryl liquid	Discontinued 5 days after screening
S50136 R50113 CRF 5105	Zyrtec liquid	Discontinued 6 days after screening
S50131 R50105 CRF 5097	Singulair and Zyrtec	Discontinued 5 days after screening
S50133 R50107 CRF 5099	Vistaril liquid	Discontinued 4 days after screening
S50126 R50120 CRF 5094	Zyrtec liquid	Discontinued 6 days after screening
S50147 R50122 CRF 5114	Rhinocort Spray	Discontinued day of screening

b. The protocol specified that a secondary measure of patient compliance would be determined by weighing the ciclesonide spray bottles to determine the amount of study drug used by each patient. According to the protocol, measurement of the amount of study medication taken between visits was calculated by comparing bottle weights from the previous study visit to the current study visits. The sponsor provided your site with a calculated range of bottle weights which represented what each bottle should weigh at T-3 and T-6 visits. Each subject received 2 bottles, labeled A and B. These consisted of either two bottles of active medication, one bottle of active medication and one bottle of placebo, or two bottles of placebo. The sponsor calculated bottle weight ranges were: 2.4 and 3.8 grams at the T-3 visit, and 4.8 and 7.5 grams at the T-6 visit. The protocol required that if patients were found to be less than 80% compliant at repeat visits, they should be withdrawn from study. Our investigation reviewed 69 of 133 subject records for compliance. Of the 69 records reviewed, 51 of 69 were found outside the range provided by the sponsor at the T-3 visit; 56 of 69 were found outside the range provided by the sponsor at the T-6 visit; only 9 of 69 were found inside the ranges provided by the sponsor at both the T-3 and T-6 visits. For example:

   i) For Subject #5092, Bottle A contained drug weight of 0.732 grams and Bottle B contained 0.695 grams at the T-3 visit; Bottle A contained 2.464 grams and Bottle B contained 2.133 grams at the T-6 visit. These bottle weights do not fall within the targeted bottle weight ranges that were designated by the sponsor to ensure 80 percent compliance, and yet this data was used in the efficacy evaluation at this site.

ii) For Subject #5091, Bottle A contained drug weight of 1.82 grams and Bottle B contained 1.215 grams at the T-3 visit; Bottle A contained 2.746 grams and Bottle B contained 2.101 grams at the T-6 visit. These bottle weights do not fall within the targeted bottle weight ranges that were designated by the sponsor to ensure 80 percent compliance, and yet this data was used in the efficacy evaluation at this site.

2. **You failed to maintain adequate and accurate case histories that record the disposition of the drug [21 CFR 312.62(a)].**

   Specifically, our investigations found discrepancy in drug accountability records for bottles received at the site (288), bottles dispensed (274), bottles returned to the site (261), and bottles returned to the sponsor (265).

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 must 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 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 Leslie Ball, M.D., at (301) 827-5455, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

Leslie 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gary DellaZanna
2/8/2007 03:52:41 PM

Leslie Ball
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