DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Lawrence S. Kim, M.D.
10103 Ridge Gate Parkway, #321
South Denver Gastroenterology
Lone Tree, CO 80110

Ref: 06-HFD-45-1101

Dear Dr. Kim:

Between May 30, 2006 and June 8, 2006, Ms. Linda Cherry, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of a clinical investigation (protocol [redacted] entitled "A Multi-Center, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate the Long-Term Safety and Tolerability of Repeated Administration of Adalimumab in Subjects with Crohn's Disease") of the investigational drug adalimumab, performed for Abbott Laboratories.

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. We are aware that at the conclusion of the inspection, Ms. Linda Cherry presented and discussed with you Form FDA 483, Inspectional Observations. Your July 11, 2006 response to Form FDA 483 does not adequately address these deficiencies. We wish to emphasize the following:

1. **You failed 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 under your care; and ensuring control of drugs under 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 qualified to perform them, 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, and in a manner that protected the rights, safety, and welfare of human subjects.

Our investigation found numerous violations in all six subjects you enrolled into the above-referenced clinical investigation (see items 2-4 below). In your written response to the 483 observations, dated July 11, 2006, you stated your belief that most of the deficiencies in the conduct of this study "stem for the actions of a single employee which occurred during an extended period in which no monitoring visits were conducted at [your] site." Although you state that this study coordinator "was supervised closely during training for the study, with regular monitoring visits initially…it was later determined that many of the errors occurred while this study coordinator had the primary role in the management of this study and without my being alerted to the problems in a timely manner." We remind you that as clinical investigator, you retain responsibility for the conduct of this study.

2. **You failed to conduct the study according to the investigational plan [21 CFR 312.60].**

   a. You enrolled two subjects, Subject 41805 and Subject 41806, who were not eligible for the study. In order to be eligible, subjects must be successfully enrolled in and completed one of two previous studies by the same sponsor. Baseline evaluations used to determine eligibility included a Crohn's Disease Activity Index (CDAI) which is calculated from the subject's clinical symptoms, hematocrit (HCT) and body weight. According to a monitoring report from [ ]the Contract Research Organization (CRO), dated December 19, 2005, Subject 41805 had a CDAI baseline score which did not meet protocol requirements; Subject 41806 did not have any of the protocol required laboratory work during the study, including baseline laboratory tests required to establish eligibility. Despite being ineligible, both subjects were enrolled in the study, given study medication, and participated in study visits for four months and one month, respectively, before being discontinued from the study.

   b. The protocol required certain laboratory tests at all study visits. Some of the laboratory tests such as hematocrit were used to calculate the CDAI, the primary efficacy measure, while other tests were used to assess drug safety. For example,

      i. Subject 41801 did not have laboratory tests at the Week 24 visit on August 3, 2005, the Week 36 visit on October 25, 2005, or the Week 48 visit on February

1, 2006.

ii. Subject 41802 had no CBC for the Week 8 visit on June 10, 2005.

c. The CDAI was used to determine a subject's response to the study medication. It was not consistently calculated as described in the protocol. For example:

i. For Subject 41801 there were two sets of Week 24 source documents. One included a completed form with the CDAI calculation using Week 12 hematocrit, the other Week 24 source document containing a CDAI form did not show a calculation, and a note was written on the form indicating that labs were not available to calculate Week 24 CDAI response.

For the same subject there were two sets of Week 36 source documents: one included a CDAI calculation using an arbitrary hematocrit value, the other Week 36 "Response Calculation" on the case report form (CRF) was left blank. The week 36 CRF was filled out and later crossed out indicating that no laboratory results were available to make the calculation.

For Week 48 the CDAI was not calculated because this subject failed to maintain a diary and laboratory results were not available. The electronic medical record (EMR) dated February 1, 2006 indicated, as previously noted, that the subject was instructed during the Week 12 visit that maintaining a diary was no longer necessary.

ii. For Subject 41802 the Week 36 CDAI was not calculated because hematology labs could not be run due to "age of specimens".

iii. For Subject 41804 the Week 24 (October 25, 2005) CDAI score was calculated using the wrong diary. The study coordinator used diaries from September 21, 2005 to September 27, 2005. No diary was available for the study period of October 19, 2005 to October 25, 2005.

iv. For Subject 41805 the Week 2 (August 17, 2005) CDAI score was calculated using the wrong set of laboratory values. The study coordinator used the hematocrit from the Week 2 laboratory results instead of the Baseline laboratory results.

For the same subject, the Week 4 (September 1, 2005) CDAI score was calculated using the wrong diary. The study coordinator used the diary dated August 21, 2005 to August 27, 2005 instead of August 25, 2005 to August 31, 2005.

d. Adverse Events were not always reported in the CRFs as required by the protocol. According to the protocol, any worsening of a pre-existing condition or illness was to be considered an adverse event. However, the EMR for Subject 41801, dated July 18, 2005, notes the subject called complaining of "not feeling good,

Crohn's flare-up, cramping". In addition, the EMR dated December 30, 2005 indicates "a lot of abdominal pain". These adverse events, however, were not documented in the CRF.

e. Not all visits were completed within the timelines designated in the protocol. For example,

   i. The Week 36 visit for Subject 41802 was two weeks out of window.

   ii. The Week 12 visit for Subject 41803 was three weeks out of window, while the Week 24 visit was five weeks out of window.

   iii. The Week 36 visit for Subject 41804 was four weeks out of window.

f. The EMR for Subject 41083 dated October 21, 2005 indicates in two places in the progress note that the subject is taking the test article once per month instead of every week or every other week as required by the protocol. The physician provider who conducted the visit was a sub-investigator for the study and should have been aware of the dosing schedule.

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

a. The protocol required that subjects complete a diary each week in which they listed various symptoms, and gave an assessment of the severity of those symptoms. The scores derived from these variables were used to calculate the CDAI, the measure of the primary efficacy endpoint. There were deficiencies and discrepancies in the diaries of three subjects which might have led to inaccurate calculation of the CDAI scores. For example,

   i. According to an EMR dated February 1, 2006, Subject 41801 stated at the Week 48 visit of that same date that he was advised by the study coordinator [ ] possibly in April 2005, that weekly diaries were not necessary for Study [ ] However, there were Week 24 and Week 36 diaries, dated August 3, 2005 and October 25, 2005 respectively, for this subject in the study files which were signed by the study coordinator, but not the subject.

   ii. Subject 41802 had a completed but unsigned diary for Week 8, and Subject 41803 had three completed but unsigned diaries for June 9 to June 29, 2005, all marked Week 8.

   iii. For Subject 41803 the Week 27 EMR dated October 21, 2005 indicates that the subject visited the physician and complained about having up to 25 bowel movements per day; none of the subject's diaries reflects this information.

b. According to the protocol, subjects were to document medication injections on a Subject Dosing Sheet. In a Note to File dated March 5, 2006 the study coordinator noted that subjects were not given Subject Dosing Sheets. Therefore, there is no source documentation of the time of injection or the amount of investigational drug injected for any subjects in the study.

c. The protocol required that all subjects have physical examinations at each study visit. The Physical Exam Case Report Form (CRF) signature line requires "PI's [Principal Investigator's] or SI's [Sub-investigator's] signature who is a[n] M.D." Several subjects had missing or discrepant documentation of one or more physical exams, and several had physical exam CRFs without physician signatures. For example,

   i. Subject 41806: there is no documentation in the record of a physical exam at the baseline visit of December 6, 2005.

   ii. Subject 41801: For the Week 24 visit on August 3, 2005 visit a physical exam form filled out. However, there was no physician signature and no supporting note in the source document to indicate that a physical exam had been completed by the physician.

   For the same subject at the Week 36 visit on October 25, 2005, the physical exam form is not filled out but is signed by a physician. In a Note to File dated March 3, 2006 the study coordinator states that the physician can't recall the physical exam and therefore can't comment on whether it was performed.

d. Concomitant therapy was not always reported in the CRFs as required by the protocol. For example,

   i. The EMR for Subject 41801 dated December 30, 2005 indicates subject was on Azathioprine and that a refill was called into the pharmacy. This drug was not reported on the Other Medications and Supplements CRF.

   ii. The Week 24 EMR for Subject 41802, dated October 18, 2005, indicates Valacyclovir and Azathioprine Oral were prescribed to the subject; however, there was no reference to those medications in the concomitant therapy documentation.

   iii. The EMR for Subject 41803, dated May 12, 2005, indicates Hydromorphone was prescribed. Prescriptions dated November 9, 2005, and November 30, 2005 indicate Dilaudid was prescribed for the subject. Neither medication was reported on the Other Medications and Supplements CRF.

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

   a. Two study drug kits 114859 and 114860 (Lot[ ]could not be accounted for. The kits were reported lost by the study coordinator[ ]

   b. According to the protocol, sharps containers for expelled syringes were to be returned by subjects at each visit for drug accountability and compliance purposes. Our investigation found that subjects were not instructed by the study coordinator to bring in sharps containers holding used syringes to account for used or damaged syringes and medication disposal forms were incomplete for all 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. We acknowledge your assurances that corrective actions will be taken to prevent similar findings from occurring in any future studies. Any response and all correspondence will be included as a permanent part of your file.

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,

1/12/07

Gary Della Zanna, D.O., M.Sc.
Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research