

86719C



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Frederick C. Whittier, M.D.
4565 Dressler Rd. NW, Suite 103
Canton, OH 44718

Ref: 08-HFD-45-1201

Dear Dr. Whittier:

Between August 22 and September 12, 2007, Mr. Stephen Kilker, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations of the investigational drugs

[redacted] and [redacted] performed for [redacted]

[redacted]

- Protocol [redacted] entitled "A phase 2, multicenter, open label, titration study to assess the efficacy, safety, and tolerability of [redacted] in doses up to 200 mg BID in patients with type 2 diabetes mellitus not optimally controlled with previous treatment with one oral antihyperglycemic agent;"

[redacted]

- Protocol [redacted] entitled "A randomized, double-blind, placebo-controlled, parallel group study of the safety and reduction of signs and symptoms during treatment with [redacted] versus placebo in combination with methotrexate in patients with moderate to severe active rheumatoid arthritis and an inadequate response to previous anti-[redacted] therapy;" and
- Protocol [redacted] entitled "Long-term extension study of safety during treatment with [redacted] in patients completing treatment in [redacted] core studies."

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 October 8, 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 and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Kilker presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to conduct the clinical investigations according to the investigational plans [21 CFR 312.60].

Regarding Protocol []

- a. Of nine subjects randomized in Protocol [] three subjects met exclusionary criteria, but were not excluded from the study. The details for these subjects are described below:
 - i. Subject [] met the exclusionary criterion for previous treatment with an investigational agent, and therefore was not eligible for the study. Specifically, this subject received treatment with another study drug until August 17, 2005, less than 5 half-lives prior to screening, an exclusionary criterion. Protocol [] specifies the exclusionary criterion for previous treatment with any investigational agent as treatment within four weeks (or five half-lives of the investigational drug, whichever is longer) of screening. Subject [] was in a prior study under your conduct [] in which he received his last study drug dose on August 17, 2005. The investigator brochure (IB) for Study [] (version date August 9, 2005) found at your clinic during the FDA audit states that the half-life of [] in patients with rheumatoid arthritis (RA) is approximately 13 days. Based on a half-life of 13 days, Subject [] was not eligible for study screening until 5 half-lives, or 65 days, following the last dose of [] on August 17, 2005. However, Subject [] screening date for Study [] was September 28, 2005, only 42 days following his last dose of [] [last dose of [] on 8/17/2005 to screening date of 9/28/2005 = 42 days]. In your October 8, 2007 response letter, you noted that at the time Subject [] entered into Study [] the half-life of [] was not known. You mentioned that the half-life of [] was provided in the IB Version 12, dated February 26, 2007, but this was received after the subject was already enrolled. However, the investigator's brochure dated August 9, 2005 was found at your clinic during the FDA audit, as mentioned above. This August 9, 2005 version of the IB states that the half-life of [] in RA patients is approximately 13 days.
 - ii. Subject [] medical history documents the use of cyclophosphamide (Cytosan®), an exclusionary previous treatment, for several months in 1998. Protocol [] specifies that any previous treatment with alkylating agents, such as cyclophosphamide, is exclusionary. Subject [] was enrolled in Study [] and received the first dose of

study drug on October 31, 2005. The sponsor's Protocol Exception, Violator/Deviator Form dated November 22, 2005 notes that Subject _____ received twice daily oral doses of cyclophosphamide (Cytosan®), 100 mg in March and April 1998, and 100 mg once daily from May to September 1998. In your October 8, 2007 response letter, you state that the length of time Subject _____ was on Cytosan® was measured in weeks, not months. The subject's medical records contradict this assertion and, in any event, the protocol states that any prior use of alkylating agents is exclusionary.

- iii. Subject _____]received an injection of Kenalog® (triamcinolone) on January 17, 2006, in violation of the protocol. Protocol [_____]specifies that intra-articular or parenteral corticosteroids administered within six weeks prior to baseline are exclusionary. Subject _____ baseline visit was February 23, 2006. A January 17, 2006 medical record documents that the subject received an injection of Kenalog® in the right shoulder during a clinic visit. A March 23, 2006 note to file states that during a routine chart review it was noted that Subject _____ received a joint injection on January 17, 2006, and that the research nurse was not aware of this injection at screening. Your October 8, 2007 response letter states that the Kenalog® injection was not known to the study coordinator at the time of screening. You indicate that the subject did not relay this information to the study coordinator, and at the time of screening, the January 17, 2006 medical record dictation was not present in the subject's chart. However, below the January 17, 2006 progress note documenting the Kenalog® injection, a handwritten note dated February 6, 2006 states that the "study nurse will call patient when new arm of study opens up to be screened," indicating that the patient's medical records did reflect the Kenalog® injection prior to screening on February 9, 2006. As the clinical investigator, it is your responsibility to ensure compliance with protocol-specified eligibility criteria.
- b. Of nine subjects randomized in Protocol [_____]two subjects did not meet eligibility requirements. These subjects were not excluded from the study. The details for these subjects are described below:
 - i. Subject _____]prednisone dose was greater than 10 mg/day within 6 weeks of baseline, in violation of the protocol. Protocol [_____]specifies that oral corticosteroids (≤ 10 mg/day prednisone or equivalent) are permitted if the dose has been stable for at least 6 weeks prior to baseline. However, Subject _____'s medical records document the subject's prednisone dose as 10 mg in the morning and 5 mg in the evening on November 15, 2005, 22 days prior to the subject's randomization date of December 7, 2005. The same record contains a physician recommendation that the subject decrease his prednisone dose to 5 mg bid to qualify for this study. Accordingly, this subject's prednisone dose was not stable for a sufficient amount of time prior to baseline and exceeded the dose permitted by the protocol (10 mg/day). You did not address this violation in your October 8, 2007 response letter.

- ii. Subject [redacted] prednisone dose was not stable for the requisite time prior to baseline. As stated above, Protocol [redacted] specifies that oral corticosteroids (≤ 10 mg/day prednisone or equivalent) are permitted if the dose has been stable for at least 6 weeks prior to baseline. Subject [redacted] baseline visit was February 14, 2006. A January 25, 2006 medical record for this subject states that “she discontinued her prednisone for lack of efficacy but the dose was 5 mg twice weekly.” The note documents that the physician recommended a prednisone dose of 2.5 mg – 5 mg q a.m. at this visit. The “Con Meds” form for this subject dated February 6, 2006 lists the prednisone dose as 2.5 mg per day. None of the medications on the list has a date recorded in the “start date” column. Also, the case report form identifying previous and concomitant treatments documents the prednisone dose as 2.5 mg per day, with no start date recorded. A note to file dated October 16, 2006, and signed on October 23, 2006, approximately 8 months after Subject [redacted] baseline date, states that the prednisone dose on the January 25, 2006 physician progress note should read prednisone 2.5 mg every day. The note to file states that per Subject [redacted] prednisone 2.5 mg daily was started on December 10, 2005. In your October 8, 2007 response letter, you reiterate that the subject began a 2.5 mg daily dose on December 10, 2005, more than 6 weeks before the baseline visit on February 14, 2006. However, this information, recorded months after the fact, is in conflict with the physician's note apparently written at or about the time of the subject's January 25, 2006 visit.

Regarding Protocol [redacted]

- c. Subject [redacted] was treated with an oral antibiotic within two weeks prior to baseline, in violation of the protocol, and was not excluded from the study. Subject [redacted] rolled over to the long-term extension study, Study [redacted] on May 31, 2006. Protocol [redacted] specifies that any major episode of infection requiring treatment with oral antibiotics within two weeks prior to baseline is exclusionary. The May 31, 2006 week 24 withdrawal visit record for Study [redacted] documents that the subject was treated for a respiratory infection with Factive® (gemifloxacin mesylate) 320 mg po starting on May 24, 2006 for 7 days. The corresponding CRF page documents the start and end dates for this antibiotic as May 23, 2006 and May 27, 2006, respectively. You did not address this observation in your October 8, 2007 response letter.

Regarding Protocol [redacted]

- d. Subject [redacted] had an elevated liver enzyme (ALT) result on a sample drawn November 9, 2006 that met the protocol criteria for retesting within one week. However, the requisition for the retest sample on November 14, 2006 was erroneously marked for “lipid panel” instead of a liver panel, which resulted in the ALT retest on November 21, 2006, outside the protocol-specified retesting window of one week. Specifically, Protocol [redacted] requires that ALT values greater than three times the upper limit of normal are to be re-measured within

one week. If the elevation is confirmed, treatment with the study article must be stopped and the subject withdrawn. The upper limit for ALT as specified by the central study laboratory was 34. Subject [redacted] ALT result on a sample from 11/9/2006 was 108, meeting the criterion of greater than three times the upper limit of normal. The ALT result was received by the clinical study site on November 13, 2006. Retesting performed on November 21, 2006 resulted in a value of 135. The subject was discontinued due to medication-induced liver enzyme elevation on November 21, 2006, but had continued to take the study article until November 20, 2006. Your October 8, 2007 response is acknowledged and the clerical error in the retest sample is noted. However, the retesting was not performed within the timeframe specified in the protocol, potentially exposing the subject to harm.

2. 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)].

Regarding Protocol [redacted]

- a. A study coordinator retroactively made changes to joint counts performed by assessors in many cases long after the original assessments. Examples of swollen and tender joint counts that were changed after the original dates of assessment are provided in the table below:

Subject	Original Assessor	Date of Original Assessment	Changed By	Date of Change of Assessment
[redacted]	[redacted]	12/7/05: Baseline visit	[redacted]	1/16/06
[redacted]	[redacted]	4/12/06: Escape Week 18	[redacted]	4/24/06
[redacted]	[redacted]	2/6/06: Screening visit	[redacted]	4/26/06
[redacted]	[redacted]	2/14/06: Baseline visit	[redacted]	4/24/06
[redacted]	[redacted]	2/28/06: Week 2 visit	[redacted]	2/28/06 and 4/24/06
[redacted]	[redacted]	3/14/06: Week 4 visit	[redacted]	3/30/06 and 4/24/06
[redacted]	[redacted]	7/6/06: Week 20 visit	[redacted]	7/24/06
[redacted]	[redacted]	2/23/06: Baseline visit	[redacted]	3/13/06

Your October 8, 2007 response letter states that attempts to correct the case report forms were made in response to a query from the sponsor. However, you did not explain how the corrected assessments were determined long after the original assessments were performed. Additionally, you pointed out that Subject 5924 had a non-evaluable joint that had consistently been reported, and corrections were made as a result. However, additional changes were made to this subject's assessment that did not pertain to the non-evaluable joint.

Regarding Protocol [redacted]

- b. A new PK (pharmacokinetic) sample preparation record was made for Subject [redacted] and the original was discarded with no adequate explanation. Information on the original record had been questioned by the sponsor's monitor,

and based on a November 2, 2006 monitoring letter, the newly created record contained information that was previously not present on the original record. Specifically, a letter from the sponsor monitor dated October 10, 2006 stated that the [] sample at Week 4 for Subject [] was marked not done in the eCRF, but the source PK log was completed stating the centrifugation time and processing details for the sample. Per the monitor's request, the sample processing information on the PK log was deleted during the visit, and this change was initialed and dated. However, following the next monitoring visit, the monitor pointed out in a November 2, 2006 letter that the PK log for Subject [] was not the same log she saw at the previous monitoring visit. The monitor wrote that the changes she witnessed at the previous visit were missing from the newly created log, and the [] sample was labeled as "not done" on the new log. The newly created log also contained all the PK processing information which was noted as missing at the previous monitoring visit. This PK processing information was not found in the subject records, although it is crucial source documentation. In your October 8, 2007 response letter, you acknowledged that the original log was created, and stated that the original was discarded as it was "illegible" due to a coffee spill. You also stated that you have addressed this issue with your staff. However, you did not provide an adequate explanation for the new information contained on the newly created log that had not been present on the original record.

- c. For Subject [] visit on August 31, 2006, source and progress notes appear to have been written and signed by a study coordinator, but the study coordinator was not at the office that day. In your October 8, 2007 response letter, you acknowledged that the study coordinator was hospitalized at the time, and you and another staff member performed the subject's visit. Additionally, you acknowledged that the study coordinator back-dated the notes to the day of the visit rather than the day the notes were written. You note that you addressed this issue with your staff, and we acknowledge that you wrote a Note to File to clarify that the progress note was actually written on September 5, 2006.
- d. Records of processing of PK samples were not kept adequately through October 3, 2006. A November 28, 2006 Note to File states that PK processing information for all four subjects ([] [] [] []) had not been recorded and the information could not be verified from study start through October 3, 2006. We note that you acknowledged this observation in your October 8, 2007 response.

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

Page 7 – Frederick C. Whittier, M.D.

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 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:

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations, Bldg. 51, Rm. 5354
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
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/

LESLIE K BALL
03/06/2008