



CBER-00-023

JUN 20 2000

Center for Biologics Evaluation and
Research
1401 Rockville Pike
Rockville MD 20852-1448**WARNING LETTER****CERTIFIED MAIL**
RETURN RECEIPT REQUESTED

Howard R. Terebelo, D.O.
Providence Cancer Center
22301 Foster Winter Drive
Southfield, Michigan 48075

Dear Dr. Terebelo:

During an inspection ending on April 19, 2000, Ms. Lisa Oakes, an investigator with the Detroit District Office of the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study, sponsored by _____, using _____ interleukin _____ in adult cancer patients. The inspection was conducted under FDA's Bioresearch Monitoring Program that includes inspections designed to monitor the conduct of clinical research involving investigational drugs.

Based on information obtained during the inspection, we have determined that you have violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations, Part 312 [21 CFR 312] (copy enclosed). Our investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of unlicensed investigational new drugs for the reasons listed below. The applicable provisions of the CFR are cited for each violation.

1. Failure to ensure that the investigation is conducted according to the signed investigational plan (protocol). [21 CFR 312.60]

Our inspection revealed that several important protocol directives were not followed, resulting in significant deviations from the protocol as follows:

A. Subject Eligibility

Class III-IV congestive heart failure is an exclusion criteria, however, subject — was enrolled in the study on 12/14/95 with Class III-IV congestive heart failure (diagnosed 10/3/95). There was no documentation that the sponsor provided an exception for this subject.

We view the enrollment of ineligible subjects as a serious protocol deviation. Entry/eligibility criteria must be critically reviewed to protect the safety and welfare of study subjects. Treatment of subjects outside the approved protocol may affect the final safety and efficacy results of the study.

B. Study Procedures

1. The protocol requires — complete blood counts (CBCs) if the platelet count falls to — or lower. This was not performed for 2 subjects as follows:
 - a. On study day 19, subject — had a platelet count of 23,000 but a CBC was not drawn for the next 3 days (study days 20, 21, 22); the Hematology CRF states that on study day 20, subject — did not show up for labs, however, no explanations are provided for study days 21 and 22.
 - b. Subject — had a platelet count of 18,000 on study day 8, however, a CBC was not done on study day 9. On study day 10, subject — had a platelet count of 28,000, however, no platelet count was done on days 11 or 12. No explanation is provided to explain why the CBCs were not done.
2. The protocol requires that subjects have a CBC on the first day of study drug administration and —times — with no more than — days between each CBC. Subject — did not have a CBC until the 6th day of study drug administration (7/31/96) and subject — did not have a CBC for 3 consecutive days (2nd, 3rd, and 4th days of study drug administration).
3. The protocol requires that — exams be given within — days prior to the start of the study drug and within — days of the last dose of the study drug. Subject — received an — exam on 2/15/96 which was 28 days before the start of the study drug on 3/14/96. No exam was performed within — days of the last dose of the study drug.
4. The protocol required chest x-rays within — days of starting the study drug and within 1 to 3 weeks after the last dose of the study drug. Subjects — and — did not have the follow-up chest x-ray performed.
5. The protocol required an electrocardiogram (ECG) to be performed on subjects within — days of beginning the study drug and within

_____ after the study was completed. Subject _____ did not have either of the required ECGs and subject _____ did not have the follow-up ECG.

It is your responsibility as principal investigator to ensure that all tests and evaluations are conducted at the time points indicated in the protocol. Missing tests, tests performed outside of protocol-specified time windows, and other missing clinical procedures can adversely affect safety and efficacy data analyses.

C. Study Drug Storage

The protocol required that the study drug be stored at 2-8 °C, however, the temperature of the refrigerator used to store the study drug was not monitored when the study was conducted. A log was implemented on 2/28/00 to monitor the refrigerator temperature, which is read once a week from a dial thermometer in the refrigerator.

2. **Failure to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation. [21 CFR 312.62(b)]**

A. Because the study records were disorganized, the FDA investigator reviewed data from the hospital blood bank and pathology records to verify transfusions received by the study subjects. Discrepancies between source documents and case report forms (CRFs) were noted for the transfusions of platelets (PLTs) and red blood cells (RBCs) received by 4 of 7 subjects during the previous chemotherapy cycle and the current chemotherapy cycle. The listing of subject _____ on the CRF as having received no platelet transfusions during the previous chemotherapy cycle when source documents indicate that this subject received 2 platelet transfusions resulted in the incorrect placement of this subject in stratum A during randomization. The discrepancies are as follows:

Transfusions - Previous Chemotherapy Cycle

Subject	Source Documents	Case Report Form
_____	2 PLT transfusion events	0 PLT transfusion events
_____	4 RBC units	8 RBC units
_____	2 RBC units	1 RBC unit
_____	4 PLT transfusion events	3 PLT transfusion events
_____	6 RBC units	2 RBC units

Transfusions - Current Chemotherapy Cycle

Subject	Source Documents	Case Report Form
—	6 RBC units	2 RBC units

- B. The concomitant medications ondansetron, Hexadrol, Prilosec, Ventolin, Aerobid, Megace, Atrovent, and Elavil were listed on the CRF for subject — but were lined out and initialed with no explanation. According to the study nurse, the entries were lined out at the direction of the study monitor because they could not be verified through medication administration sheets. As the medication administration sheets were missing from the records for subject — it was not possible to determine during the FDA inspection exactly what concomitant medications the subject received. The only documents available to determine the subject's concomitant medications were the physician orders for D 5 ½, Megace, Aerobid, Vanceril, Atrovent, and Prilosec. A note to the subject's file dated 3/20/00 and signed by the study coordinator and principal investigator lists the medications noted to be in a source document but not listed on the CRF and also states that "Magic Cough Syrup" (administered 5/7/96) should be corrected to "Magic Mouthwash."
- C. In a note to the file dated 3/20/00 and signed by the study coordinator and the principal investigator, it states, with reference to subject —, that the pretreatment signs and symptoms of diarrhea (4/24-25/96) and orthostatic hypotension (4/24/96) and the adverse event of upset stomach (5/15/96) were in source documents but not listed on the CRF.

Clinical investigators are responsible for assuring that the data contained in the CRFs are complete and accurate. Case report entries should be checked against source documents, medical charts and laboratory results by the principal investigator. Inaccuracies found in CRFs are the investigator's responsibilities.

Proper procedures for correcting records include showing the changes and indicating when the changes were made, the reason for the change, and who made the changes. Errors should be crossed out by a single line but not obliterated, the correction inserted, and the change initialed and dated by the individual making the change. Explanations for the change should be provided either adjacent to the change or in a note to the file prepared when the change is effected.

3. Failure to promptly notify the Institutional Review Board (IRB) of serious adverse events. [21 CFR 312.66]

Serious adverse events were not reported to the IRB in a timely manner or were

not reported. For example:

- A. Subject — experienced failure to thrive on 4/15/96 and was hospitalized for 10 days, which was classified as a serious adverse event. The adverse event was reported to the study sponsor on 4/19/96, however, it was not reported to the IRB until over one year later (8/6/97).
- B. Subject — developed dehydration on 5/17/96 and was hospitalized for 5 days, which was classified as a serious adverse event. This was reported to the sponsor on 5/17/96, but was never reported to the IRB.

Your signature on Form FDA 1572, Statement of Investigator, indicates your agreement to comply with all requirements regarding the obligations of clinical investigators conducting human clinical trials and all other pertinent requirements in 21 CFR Part 312. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan (protocol), and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

You deviated from an authorized study plan, investigator statement, and other conditions imposed on the study by the IRB or federal regulations. Deviations in the conduct of this study appear to be the result of your lack of understanding of the procedures and requirements that govern the use of investigational new drugs. Good Clinical Practice (GCP) is essential to maintain the quality of data collection during the conduct of clinical trials. All personnel assisting in the conduct of a clinical study should be trained in GCP. The principal investigator has the responsibility to review study work that is delegated, particularly clinical decisions, and must ensure that study staff are following the investigational plan (protocol). The principal investigator should meet periodically with the team of clinicians and non-clinicians participating in the study to discuss study progress and problems and ensure that minutes of these meetings are maintained.

The discrepancies found in the study records indicate a lack of attention to effective record keeping practices. As the clinical investigator responsible for these trials, you must actively review the subject files including the CRFs. Clinical investigators are responsible for assuring that the data contained in the CRFs and submitted to the sponsor are complete and accurate. Investigators are also responsible for supervising the study coordinator and other assistants who complete CRFs and process queries.

This letter is not intended to be an all inclusive list of deficiencies with your clinical study of investigational _____ interleukin _____. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations. We request that you inform us, in writing, within fifteen (15) business days after the receipt of this letter, of the steps you have taken or will take to correct these violations to prevent the recurrence of similar violations in current and future studies. If corrective

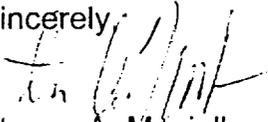
action cannot be completed within 15 business days, state the reason for the delay and the time within which the corrections will be completed. Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include but are not limited to initiation of clinical investigator disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs.

Please send your written response to:

Dr. Patricia E. Hasemann (HFM-664)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448
Telephone: (301) 827-6337

If you require additional time to respond, or have any questions concerning this matter, please contact Dr. Hasemann at the telephone number above.

Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosure: 21 CFR Part 312

cc: _____

Chairman, Institutional Review Board
Providence Hospital
16001 West Nine Mile Road
Southfield, MI 48037