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Food and Drug Administration  
Center for Biologics Evaluation and Research  
1401 Rockville Pike  
Rockville MD 20852-1448

MAR 13 2002

By Certified Mail - Return Receipt Requested  
And By Facsimile Transmission

CBER-02-009

Warning Letter

Michael L. Gruber, M.D.  
New York University Medical Center  
530 First Avenue, Suite 9S  
New York, New York 10016

Dear Dr. Gruber:

Between June 5 and 22, 2001, Mr. Thomas P. Hansen, an investigator with the Food and Drug Administration (FDA) New York District Office, conducted an inspection of the following clinical studies sponsored by \_\_\_\_\_ in which you participated:

- (1) Protocol \_\_\_\_\_  
\_\_\_\_\_ at a Dose of 50 µg/kg Subcutaneously Once Daily for 14 Days vs. Placebo in Adult Cancer Patients with Severe Thrombocytopenia Due to Chemotherapy"
- (2) Protocol \_\_\_\_\_  
\_\_\_\_\_ in Adult Cancer Patients with Severe Chemotherapy-Induced Thrombocytopenia Who Have Completed Protocol \_\_\_\_\_

This inspection was conducted under FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational drugs.

Deficiencies noted during the inspection are listed on the Form FDA 483, Inspectional Observations, presented to you at the conclusion of the inspection. We have reviewed your written response dated July 26, 2001, addressed to Mr. Hansen, to the Inspectional Observations. Although your letter explains some of the study deviations and provides supporting documentation and corrective actions, we request that you specifically respond to the items designated with the symbol "→→" that are included below.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs as published under Title 21, Code of Federal Regulations (CFR), Part 312 [21 CFR 312] (available at <http://www.access.gpo.gov/nara/cfr/index.html>). The applicable provisions of the CFR are cited for each violation listed below.

- 1. You failed to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation, and you failed to retain investigational records. [21 CFR § 312.62(b) and (c)].**

You failed to maintain source data (e.g., subject diaries, hematology reports, transfusion records) and case report forms (CRFs) for protocols \_\_\_\_\_ and \_\_\_\_\_

Your letter acknowledges the missing CRFs and subject diaries, and states that in 1999, the study regulatory binders, diaries, and CRFs were lost or misplaced after they were sent to another facility while your office underwent renovation. You also state that you have asked certain other parties, e.g., the NYUMC Blood Bank, to send you copies of missing records. Your proposed corrective actions include maintaining subject charts at your office, reviewing and initialing correspondence received from the sponsor, and obtaining a receipt for all CRFs, diaries, data records and regulatory binders sent to other facilities for storage. Please note that you must ensure that the records, no matter where they are physically stored, are retained for 2 years following the date of application approval of the drug for the indication for which it is being investigated; or if no application is to be filed, or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified. →→Please indicate in your response whether you have received copies of the transfusion source data and laboratory reports requested from other parties and what corrective measures you are implementing for future studies to ensure receipt of copies of laboratory reports or other study procedures whether performed at your facility or at outside facilities.

Your letter states that the complete blood count (CBC) laboratory work for subject — was performed at an outside laboratory and includes, as attachment 11, a sheet stated to be the report from the outside laboratory. The submitted sheet appears to be a summary of the patient's laboratory results for red blood cells, white blood cells, platelets, and "HGN" for the period 02/29/96 to 06/17/96. This sheet does not appear to be source data for laboratory work. It bears an abbreviated subject name, does not identify the laboratory performing the work, and does not provide all the CBC data required on the CRF.

**2. You failed to ensure that the investigation is conducted according to the signed investigational plan (protocol). [21 CFR § 312.60].**

The inspection revealed that there were many deviations from the protocol requirements for study procedures. Even though there were only — subjects enrolled in protocol ' — , numerous study procedures were not performed or were not performed with the frequency or within the time frame required by the protocol. Examples are as follows:

**A. Protocol ' —**

(1) Protocol ' — emphasized that the performance of CBCs according to the required schedule was critical to the success of the study. There was no documentation that CBCs were performed as required for the following subjects:

- a. Subject — received only 2 CBCs per week for the weeks 04/22/96 and 04/29/96, although the protocol required the CBCs to be performed at least 3 times weekly (platelet count  $\geq 30,000$  cells/ $\mu$ L and  $\leq 100,000$  cells/ $\mu$ L).

Your letter acknowledges this deviation.

- b. There are no supportive laboratory data for CBCs conducted on 07/01/96 and 07/02/96 listed in the "hematology tests" case report form for subject —
- c. CBCs were not performed for subject 84 for the period 10/03/96 through 10/06/96, although required by the protocol.
- d. Subject — received the final dose of study drug on 10/29/96. A follow-up CBC on 11/01/96 indicated that the platelet count was 18,000 cells/ $\mu$ L, however, daily

CBCs were not continued as required by the protocol until the platelet count was  $\geq 30,000$  cells/ $\mu\text{L}$ . In addition, a period of 4 days lapsed after the CBC done on 11/06/96 (platelet count 48,000 cells/ $\mu\text{L}$ ) before the next CBC was done on 11/11/96. The protocol required the CBC to be performed at least 3 times weekly on nonconsecutive days with no more than 2 days between each CBC when the platelet count was  $\geq 30,000$  cells/ $\mu\text{L}$  and  $\leq 100,000$  cells/ $\mu\text{L}$ .

Your letter acknowledges these deviations.

- (2) Protocol [redacted] required ophthalmologic exams within 14 days prior to the start of the study drug and within 3 days of the last dose of the study drug. Ophthalmologic exams were not performed on subjects [redacted] within 3 days of the last dose of the study drug. In addition, the tonometry exam was not performed on subject [redacted] as part of the ophthalmologic exam during Visit 0 on 06/13/96.

Your letter acknowledges that final ophthalmologic exams were not performed on subjects [redacted]. However, you state that a final ophthalmologic exam was performed on Subject [redacted] and that there is documentation that subject [redacted] refused the tonometry exam and the ophthalmologic exam on the study day required by the protocol.

We have reviewed the attachment you submitted in support of your explanation for subject [redacted]. The documentation provided is for a funduscopy exam dated 11/01/96 performed during the subject's participation in protocol [redacted], the open-label study for subjects who completed protocol [redacted]. This exam was not performed within 1-3 days after the last dose (10/16/96) of the study drug as required by protocol [redacted] and was not a full ophthalmologic exam. Although you state that the refusals of subject [redacted] were documented, no documentation was included in your letter. You also indicate that in the future, documentation of subject refusals will improve.

- (3) The protocol required an electrocardiogram (ECG) within 14 days before the start of the study drug and within 1-3 weeks after the last dose of the study drug. ECGs were not performed as required or were not documented in the source data as being performed for the following subjects:

Subject	Required ECG Tests Not Done (ND); Not Performed When Required (NPWR); or No Source Data (NSD)
—	final ECG (NSD)
—	pre-study and final ECG (ND)
—	pre-study and final ECG (ND)
—	pre-study and final ECG (NPWR)
—	final ECG (ND)
—	final ECG (ND)
—	pre-study ECG (ND)

Your letter acknowledges that the required ECGs were not performed as cited above for subjects —

— For subject —, you agree that there was no pre-study ECG and you do not comment on the failure to perform the final ECG within 1-3 weeks after the last dose of the study drug. You state that you have been unable to obtain copies of the ECG results for subject — performed at an outside institution but will document inability to obtain study results from outside institutions in future studies. This response is not adequate because your conduct of the protocol should ensure that copies of source documents for laboratory or other study procedures are obtained even though these procedures are performed by an outside facility. Failure to obtain source documentation required by the protocol may jeopardize study subject welfare and the integrity of trial data collected.

- (4) The chest X-ray required within 1-3 weeks after the last dose of the study drug was not performed or was not documented in source data as being performed for subjects —

Your letter acknowledges the failure to perform the chest x-rays in subjects — and the inability to document the final chest x-rays performed for subjects —

— You state that in the future you will document the inability to obtain documentation of study procedures performed by outside institutions. This response is not adequate as discussed under item 3 above.

- (5) Blood chemistry evaluations were not performed for subject — on the day of the last study dose and during the follow-up visit, although required by the protocol, or for subject — within 3 days before the start of chemotherapy as required by the protocol.

Your letter acknowledges that the cited blood chemistry evaluations were not performed.

B. Protocol \_\_\_\_\_

Your letter states that you believe that observations 37-40 listed on the Form FDA 483 are not correct, because the treatment dates for the subjects do not correspond to the treatment dates listed in the report. We acknowledge the treatment dates cited in your response.

During our review of the CRFs for protocol \_\_\_\_\_ collected during the inspection, we noted protocol deviations or a lack of source data for these treatment dates. →→We request a response on the following:

Subject	Dates Treated	Protocol Procedure Not Done (ND) or No Source Data (NSD)
—	05/23-06/06/96; 06/21-07/05/96	cycle 1-06/18/96 follow-up chest x-ray, temperature, pulse, and respiration (ND); IL-11 blood specimens (ND) on days 1, 7-9, last dose, and follow-up; hematology (ND) on 06/08, 10, 30 and 07/01, 04/96; chemistry laboratory tests (ND) on 05/30/96 (cycle 1, day 7-9), 06/05/96 (cycle 1, day 14), 06/27/96 (cycle 2, day 7-9), 07/05/96 (cycle 2, last dose), and 07/24/96 (cycle 2, follow-up); cycle 1 last dose fundoscopic exam (ND)
—	11/01-06/96	cycle 1 follow-up chest x-ray (ND); hematology tests on 11/15, 18, 21/96 (NSD)
—	11/13-26/96	day 1 temperature, pulse, and blood pressure (ND); 12/18/96 follow-up visit vital signs, physical examination, chest x-ray (ND); IL-11 blood specimen on day 7-9 (ND)
—	12/04-17/97	day 1 temperature, pulse, respiration (ND); chemistry laboratory test on last dose day (ND); chest x-ray, chemistry and hematology during follow-up visit (ND)

3. 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. Record review at the research pharmacy revealed that the study drug for subject — was released from the pharmacy on 04/23/96.

Subject  $\bar{1}$  received the study drug on 04/24/96. The prescription, however, is dated 04/25/96. →→ Please explain this discrepancy.

- B. Subject  $\bar{1}$  received the study drug from 06/20/96 to 07/03/96 (14 days), and according to the protocol should have used 14 vials of the study drug. However, the drug accountability CRF (06/20/96) and drug accountability record indicate that subject  $\bar{1}$  was dispensed and used 15 vials of the study drug. Your letter states that you are unable to confirm records which indicate that the subject used 14 units of study drug and that 1 vial was unaccounted for due to the loss of the subject diary.

During the inspection, it was also noted that the oncology nurse practitioner was not listed on the Form FDA –1572 as a sub-investigator, although she was responsible for subject dosing and scheduling laboratory procedures. Sub-investigators are considered to be any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions. As the oncology nurse practitioner was a member of the trial team and was responsible for critical trial-related procedures, she should have been listed on the Form FDA-1572.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations.

Your letter proposes steps to correct the inspectional observations concerning protocol non-adherence and failure to ensure the retention of study records. These steps include participation by yourself and study personnel in courses to ensure compliance with good clinical practices (GCPs), obtaining a receipt for study documents sent to off-site storage, meetings with the study monitor, and adherence to the general responsibilities of investigators including assurance of IRB review and record keeping and retention requirements. As part of your response to this letter, please provide an update on the implementation of your proposed corrections, including documentation of GCP training and assurance that documents sent to other facilities for storage will be retained for the period required by the regulations.

Please notify this office, in writing, within fifteen (15) business days of receipt of this letter, of the specific actions you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. If corrective action cannot be completed within 15 business days, state the reason for the delay and the time within which corrections will be completed.

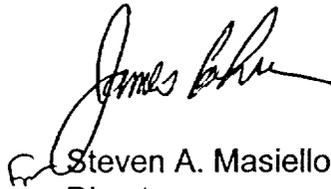
Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs, and/or injunction.

Please send your written response to:

Dr. Patricia E. Hasemann (HFM-664)  
Office of Compliance and Biologics Quality  
Food and Drug Administration  
1401 Rockville Pike  
Rockville, Maryland 20852-1448  
Telephone: (301) 827-6337

We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,



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

cc: Dr. Keith Krasinski, Chairman  
Institutional Review Board of Research Associates  
New York University Medical Center  
550 First Avenue  
New York, New York 10016

Mr. Jerome Woyshner, District Director  
Food and Drug Administration  
158-15 Liberty Avenue  
Jamaica, New York 11433