



FEB 22 2001

WARNING LETTER**By Certified Mail - Return Receipt Requested**

CBER-01-014

Michael R. K. Jacoby, M.D.
Mercy Ruan Neurology Clinic
1111 6th Avenue, West Building, Suite 400
Des Moines, Iowa 50134-2611

Dear Dr. Jacoby:

During an inspection ending on November 3, 2000, Mr. Carl J. Montgomery, an investigator with the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study entitled, "A Phase III, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of [redacted] (LeukArrest™) in Patients with Acute Ischemic Stroke (HALT Stroke Trial)." [redacted]

The inspection is part of FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of research involving investigational drugs.

The deficiencies noted during the inspection are listed on the Form FDA 483, Inspectional Observations, presented to you at the conclusion of the inspection (enclosed). We reviewed your written response dated November 3, 2000, to the Inspectional Observations. Although your letter explains some of the study deviations and some corrective actions, we request that you specifically respond to the items designated with the symbol "→→" that are included below.

Based on our review of the information from the inspection, we identified deviations from applicable federal regulations as published in Title 21, Code of Federal Regulations, Parts 312 and 50 [21 CFR 312 and 50]. The deviations include, but are not limited to, the following items:

- 1. Failure to promptly report to the Institutional Review Board (IRB) all changes in the research activity. [21 CFR 312.66].**

You are a member of the IRB and you failed to keep the IRB fully informed of the activities of your study. For example,

- a. You did not inform the IRB that the sponsor temporarily suspended subject enrollment for the HALT Stroke Trial at your site on 7/7/99.

In your response letter dated November 3, 2000, you explain that you mistakenly believed that you only needed to deal with the sponsor to "make things right." You state that you developed an action plan, but acknowledge that you neglected to inform the IRB of the suspension.

- b. You failed to inform the IRB of the reasons why the sponsor closed the HALT Stroke Trial at your site on 1/18/00. The trial was terminated due to continued non-compliance with Good Clinical Practices. The following documents exhibit your failure to disclose the information to the IRB:

Your files include a letter addressed to the IRB from your Research Coordinator dated 2/6/00. This letter includes a sentence "reporting closure" of your site to the HALT Stroke Trial, but does not indicate why. This document was not found in the IRB records.

In your response letter, you explain that you did not see this letter.

- ii. A letter dated 3/29/00 to the IRB, found in the IRB records, states only the following regarding the study closure, ". . . ; Acute Stroke Trial which we have stopped participating in . . ." without reference as to why the study stopped.
- iii. In addition, the IRB on 2/24/00 apparently did not know the study was closed at your site, because the IRB approved the study for annual review on 2/24/00 as documented in a letter to you from the IRB dated 3/24/00.
- c. There is no documentation that [redacted] were sent to the IRB in a timely manner. These alerts are dated 3/10/00, 3/31/00, and 3/31/00, respectively. These documents were sent to the IRB on 10/30/00, one day prior to the start of the inspection.

You explain that your current coordinator identified this omission and submitted the safety reports.

2. Failure to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR Part 312.60].

- a. →→ Changes to the informed consent required by the sponsor in Amendment 2 version 3 of the protocol were not correctly incorporated into the consent form approved by the IRB on 8/26/99. Please explain how you plan to prevent future similar occurrences.
- b. — subjects signed the wrong version of the informed consent. For example, [redacted]

Subject _____ was randomized on 12/9/99 and signed a consent form initially approved by the IRB on 2/25/99 instead of the most recently approved version approved on 8/26/99.

In your response letter, you explain that the study coordinator included several versions of the consent form in the study binder (approved, not approved, corrected, and not corrected versions) and probably was confused as to the correct version regarding subject _____. You state that it would have been nearly impossible at that time for enrolling investigators to have known that an incorrect or non-IRB approved consent form was used.

- ii. Subject _____ was randomized and signed the consent form on 12/9/99 using the consent form approved on 2/25/99 instead of the consent form approved on 8/26/99. To correct the mistake, the subject signed version 5/5/99 of the consent form on 3/13/00. There is no documentation showing that version 5/5/99 of the consent form was approved by the IRB.

In your response letter, you explain that the study coordinator attempted to make changes to the consent form requested by the sponsor involving a single paragraph, but the coordinator deleted a small portion resulting in a wrong consent form for subject _____

→→We expect you and your institution to have in place a system that clearly identifies the current approved version of the consent form, and informs the responsible parties of the current consent form to use. One method would be to include the approval expiration date on approved consent documents with a cover notation that the document is the currently approved version.

- c. →→Informed consent documents (one approved by the IRB on 8/26/99 and those signed by subject _____, on 12/9/99, and signed by subject _____ on 12/5/99 and 3/13/00) do not include language that clearly identifies the test article as being derived from a mouse. This is important information that subjects may need to know in the event of participation in future clinical trials or treatment with murine derived products.

→→The consent forms mentioned in item "2c" above also do not include information stating that subjects who develop antibodies to mouse derived antibodies may be at risk to receive other mouse derived antibodies.

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

- a. →→The protocol requires that the National Institutes of Health Stroke Scale (NIHSS) score be obtained \leq 1 hour prior to randomization. The case report form (CRF) for day 0 (baseline) shows that the modified Rankin scale and the NIHSS for subject _____ were both started at 01:30. The test article was administered at 02:54. The initial administration of the test article was conducted 24 minutes beyond the time limits of the tests required by the protocol.
- b. →→You did not perform the Glasgow Outcome Scale score for subject _____ for day 28.
- c. →→The protocol requires that temperatures be taken every four hours through Day 3. Temperatures were not always taken. For example,
- The 32, 40, and 56 hour temperatures after the first dose of test article for subject _____, were not recorded.
- ii The 8 hour temperature on the Day 2 Temperature Monitoring form of the CRF for subject _____ was not recorded.
- d. →→Temperatures were not always taken on time for subject _____, as seen in the following table:

Temp. Times

	Projected	Actual	Early/Late
4 hrs.	06:54	06:15	Early - 39 minutes
8 hrs.	10:54	11:15	Late - 21 minutes
12 hrs.	14:54	16:35	Late - 1.5 hours
16 hrs.	18:54	18:00	Early - 54 minutes
20 hrs.	22:54	23:59	Late - 65 minutes

The initial test article administration time was 02:54 on 12/5/99.

- e. →→The Day 90 follow-up visit for subject _____ occurred on 3/13/00, nine days beyond the due date of 3/4/00 and 2 days beyond the latest date required by the protocol.

4. Failure to prepare and maintain complete and accurate case histories. [21 CFR 312.62(b)].

a →→The Medication Administration Record shows the actual times of Tylenol administration for subject _____ on 12/5/99 as 03:00, 13:00, and 22:00 hours. Corrections to the Day 0 Temperature Monitoring Page of the CRF indicate that no anti-pyretics were given to the subject on 12/5/99.

b →→There are discrepancies between the Day 0 – Day 90 Comment Log and the CRF for subject _____. For example,

Although the CRF indicates that lab samples were obtained on 6/9/99 for subject _____ on Day 2 (60 hours), the comment log reference to page 16 of the CRF indicates, "other 60 hour labs not done on 4/29/99 secondary to patient death." In addition, documentation supports the subject died on 6/10/99.

ii The comment log reference to page 9 of the CRF (Day 0 Baseline, 6/6/99) indicates, "labs sent in wrong tubes/or with wrong req [sic] forms. Therefore, results not available." However, baseline lab values dated 6/6/99 are available.

c →→There are no screening logs for the second and third weeks of June, 1999, the first and second weeks of July, 1999, and the first and third weeks of December, 1999. Subjects _____, are not identified on the available screening logs.

d →→We note a large number of requested changes by the sponsor on Case Report Form Resolution Forms and CRF Clarification Forms for the _____ subjects in your trial. Please explain how recordkeeping practices in future studies will improve upon the demonstrated level of performance in this trial.

We also note that, although you have procedures and forms for reporting subject deaths to the IRB, you failed to report such deaths in a timely manner or in a complete manner. Specifically, you did not report the deaths of subjects _____ to the IRB until 6/24/99. In addition, while you notified the IRB of the deaths of subjects _____, by letters dated 11/3/99 and 12/16/99, respectively, the information sent to the IRB was incomplete. In your response, you acknowledge procedural or other problems related to the reporting efforts of the study coordinator. In view of these problems, reliable procedures should be implemented to ensure that reporting is done in a consistent, timely, and effective manner.

In general, your response letter describes several changes that you have implemented to correct the conditions noted during the inspection. These changes include that the sub-investigators and the clinical coordinator notify you of randomizations and serious adverse events, that you are implementing weekly meetings with the study coordinator and monthly meetings with sub-investigators, that meticulous paper work is emphasized, that you will stress the importance that others keep you informed, and that you will ensure that the correct forms and letters are sent to the IRB. In addition, you made personnel changes in the study coordinator position. We also acknowledge your stated commitment to seek to meet the highest good clinical practice standards.

You are currently, or have been identified as, the clinical investigator for at least 14 studies of investigational products, and are involved in at least seven other studies. Non-compliance with the regulations governing the use of investigational drugs could affect not only the acceptability of the trial data but also the safety of the human subjects of research.

As evidenced by the deviations noted above, however, the records at your site indicate a serious failure to fulfill your responsibilities as clinical investigator, including supervision of study personnel. Staff who were delegated the authority to perform certain functions were not adequately trained or monitored. Although authority may be delegated, the clinical investigator is ultimately responsible for study conduct.

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.

Please notify this office in writing, within 15 business days of receipt of this letter, of the specific steps 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 that may render a clinical investigator ineligible to receive investigational drugs.

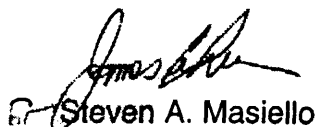
Please send your written response to:

Debra Bower (HFM-664)
FDA/Center for Biologics Evaluation and Research
Division of Inspections and Surveillance
1401 Rockville Pike
Rockville, MD 20852-1448

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Please send a copy of your response to FDA's Kansas District Office, Director, Compliance Branch, 11630 West 80th St., Lenexa, KS 66214-3338. If you have any questions concerning this matter, please contact Ms. Bower at (Tel.) 301-827-6221.

Sincerely,



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

Enclosure

Form FDA 483 dated 11/3/00

cc: Prasad Palakurthy, M.D., Chairman
Institutional Review Board
Mercy Medical Center-Des Moines IRC
1111 6th Avenue
Des Moines, Iowa 50314

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