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NOV 30 2000

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

Warning Letter

By Certified Mail - Return Receipt Requested

CBER - 01 - 004

Mark L. Batshaw, M.D.
Children's National Medical Center
111 Michigan Avenue, N.W.
Washington, DC 20010-2970

Dear Dr. Batshaw:

During an inspection conducted from November 30, 1999, to January 19, 2000, Mr. Mike Rashti, an investigator from the Food and Drug Administration (FDA) Philadelphia District Office, and Dr. Thomas Eggerman, a Medical Officer from the FDA Center for Biologics Evaluation and Research (CBER), visited the headquarters of the Institute for Human Gene Therapy at the University of Pennsylvania to examine records relating to the clinical study of an investigational adenoviral vector expressing the ornithine transcarbamylase (OTC) gene. The inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational new drugs.

Study documents show that you had a pivotal role in the conduct of the study. Although you were not responsible for all aspects of the study, you were in a position to influence how the study was conducted. The violations listed below do not reflect all of the deficiencies in the study, but identify those for which you bear some responsibility.

Based on information obtained during the investigation, 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), Parts 312 and 50 (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. Failure to ensure that an investigation is conducted according to the investigational plan (protocol). [21 CFR § 312.60].

For the purpose of this letter, the version 4 revisions (dated July, 1998, and November, 1998) to sections 4.1.1 and 4.3 do not apply because the sponsor did not submit these protocol versions to FDA, and there were therefore not part of the approved investigational plan.

- A. You did not follow the protocol requirement to stop the study as described in protocol Section 4.3, which states, "If a single patient develops Grade III or higher toxicity, the study will . . . be halted." Protocol Section 4.1.6 further states, "Evidence of toxicity will be measured using a modified version of the _____ initially developed by the _____ for chemotherapy trials." The table on page 3 identifies the adverse events experienced by the subjects enrolled in this study classified in accordance with the _____. Based on protocol section 4.1.6, Grade III or IV toxicities are categorized as "significant," and are shown in the lightly shaded portions of the table. The unshaded portions of the table denote Grade I and II toxicities categorized as "mild" by protocol section 4.1.6. The darkly shaded portions of the table indicate that no toxicities were noted.

We acknowledge that the sponsor and FDA discussed the Grade III adverse events experienced by Subjects _____ and after each report, FDA granted permission for the sponsor to enroll an additional subject. For Subjects _____ you provided an explanation that could account for the toxicities based on the subjects' medical histories.

The following Grade III toxicities did not have an explanation, and could be related to the dose of the investigational vector.

- i. You did not stop the study after Subject _____ developed Grade III liver enzyme elevation and Grade III anemia.
- ii. You did not stop the study after Subject _____ developed Grade III liver enzyme elevation and Grade III hypophosphatemia.
- iii. You did not stop the study after Subject _____ developed Grade III fever and Grade III hypophosphatemia.
- iv. You did not stop the study after Subject _____ developed Grade III fever and Grade III hypophosphatemia.
- v. You did not stop the study after Subject _____ developed Grade III fever.

SUBJECTS (*Grade*)

	cohort 1	cohort 2	cohort 3	cohort 4	cohort 5	cohort 6
thrombocytopenia	—					—
bilirubin						
transaminases (ALT or AST)						—
alkaline phosphatase or 5' nucleotides						
blood ammonia						
fibrinogen	<i>not done</i>	— <i>n.d.</i>			<i>n.d.</i>	— <i>n.d.</i>
prothrombin time						
partial thromboplastin time						
GGT (γ-Glutamyl transpeptidase)						—
Fever						
Hemoglobin						
Phosphate						

n.d. = not done

- B. Subjects who failed to meet the eligibility criteria were allowed to participate in the clinical trial. Subjects were administered the investigational vector even though they should have been excluded.
- i. Subject — was not eligible to participate in the study because the subject's baseline neutralizing antibody titer was 1280. Protocol version 3 states that subjects must have a titer less than 1280 to participate in the study. Subject — was infused with the test article approximately two weeks after February 23, 1998, when FDA specifically rejected the sponsor's proposal to discontinue the neutralizing antibody assessment as an entry criterion, during a telephone conversation with a representative of the Institute for Human Gene Therapy. The telephone conversation was documented in notes of a meeting you attended.
 - ii. You enrolled Subject — even though he had elevated ammonia levels of 114 micromoles on day -3, and 91 micromoles on day -1 in the immediate pre-infusion period, and thus did not meet the inclusion criterion. These measurements were the daily baseline ammonia measurements before N15 testing. Protocol versions 2, 3, and 4 (in effect after September 4, 1997) lists the inclusion criteria, including the following: "F. Plasma ammonia level < 70 μ M (nl 15-35 μ M)." Protocol version 0 (dated April 16, 1996) and version 1 (dated November 4, 1996) state the following: "All subjects ... plasma ammonia levels must be <50 μ M (nl 15-35 μ M) at the time of the study" (emphasis added). Serum ammonia levels are critical in the screening of potential subjects. Since a subject's condition may change suddenly in OTC deficiency, the clinically most relevant levels are those measured closest to the time of vector administration.
 - iii. You enrolled Subject — a male, as the second patient in the sixth dose cohort. This was a violation of the agreement between the sponsor and FDA that male subjects could only be enrolled as the third subject in a dose cohort. The agreement was made during a telephone conversation between Dr. James Wilson and an FDA representative on December 13, 1996, and documented in Dr. Wilson's memorandum dated December 17, 1996, to the OTC project team, which states, "The FDA requested to limit the number of male subjects per cohort to one and always have him be the third patient....I will incorporate these changes into the revised OTC protocol and informed consent documents as soon as possible which will be forwarded to the Penn, and CHOP IRBs as well as the RDA [FDA]."

- iv. You enrolled Subject — who has a hereditary liver disease. Protocol version 1 stated that patients with a “history of hepatic or vascular disease” would be excluded from the study. You eliminated this exclusion criterion from the body of the revised protocols in versions 2, 3, and 4, but you did not identify this change on the Preface list of protocol changes forwarded to FDA and the institutional review boards (IRBs). The result of the failure to disclose this revision in the list of changes is that the revision was obscured from FDA or IRB consideration, and, therefore, the revision was not part of the approved investigational plan.

 - C. During a telephone conversation on February 23, 1998, an FDA representative instructed Mr. Phil Cross, representative of the Institute for Human Gene Therapy, to allow at least 30 days, or more if necessary, between infusion of subjects to determine whether any anemia resolved before an additional subject was infused. This conversation is documented in the notes of the study team meeting, which you attended, held on February 25, 1998. On March 9, 1998, Subject — was infused with the investigational vector, fourteen days after the infusion of Subject —
- 2. You failed to assure that the Institutional Review Board would be responsible for the initial and continuing review of the clinical study by failing to submit accurate reports regarding the safety of the study, and failing to accurately and completely identify changes to the protocol for Institutional Review Board review and evaluation. [21 CFR 312.66].**
- A. You changed two entry criteria identified in protocol version 1 without IRB approval. You submitted protocol version 2 to the University of Pennsylvania IRB and to the Children’s Hospital of Philadelphia IRB on August 11, 1997. The cover letter states the following: “At the completion of this first participant cohort, we are submitting for your review Protocol Version 2.0 that contains many modifications. The Preface of the Protocol lists all modifications, but several modifications are also highlighted [in the cover letter] below.” You did not identify these changes on the Preface of the Protocol you represented as listing all changes. You listed dozens of protocol changes in the Preface of the Protocol, including other changes in the listing of inclusion and exclusion criteria in the Preface section entitled “Participant Criteria.” Yet, the following important changes were excluded:

- i. You changed the inclusion criterion of serum ammonia from less than 50 micromoles (protocol version 1) to less than 70 micromoles (in all later versions). The revised criterion was only identified on protocol page 19 in section 3.2.2.
 - ii. You eliminated the exclusion criterion of "history of hepatic or vascular disease" (protocol version 1) from all later versions. If this criterion had remained in the protocol, then Subject — should have been excluded from the study based on a hereditary dysbilirubinemia.
- B. On August 11, 1997, you submitted a progress report and request for reapproval to the University of Pennsylvania IRB which contained significant inaccuracies.
- i. You state in the cover letter that the first subject developed a mild anemia that was most likely related to the amount of blood drawn for testing. You further state that the amount of blood was decreased by about half for the subsequent subjects, and that "using this approach the following two participants did not develop anemia." This statement is incorrect because Subjects — and — also developed Grade I anemia.
 - ii. The form entitled, "Report for Reapproval of Research Involving Human Beings" reported the progress of the first three subjects who were administered the investigational vector. You answered the questions "Total number of subjects experiencing adverse effects" as "0." You did not report the Grade I and Grade II reactions experienced by each of the three subjects enrolled to date.
- C. You failed to notify the IRB of adverse events according to the provisions of the protocol sections 4.3. Section 4.3 of the protocol states, "If two patients develop mild (Grade II) toxicity, the study will be put on clinical hold until an explanation acceptable to us, the CHOP IRB, the Penn IRB, and the FDA is achieved. If a single patient develops Grade III or higher toxicity, the study will also be halted."

You failed to report the following toxicities to the Children's Hospital of Philadelphia IRB and the University of Pennsylvania IRB as required by the protocol. The protocol was very clear that these needed to be reported as each adverse event occurred.

- i. Grade II toxicities in dose cohort two -- Subjects _____
- ii. Grade II toxicities in dose cohort three -- Subjects _____

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

- A. You did not amend the informed consent document following the Grade III liver enzyme elevations experienced by Subjects _____. In the letter to FDA dated January 13, 1999, the firm's representative stated the "intention not to enroll patients with a history of previous intravenous drug administration...[and]...patients who are treated chronically with Dilantin and/or Lamictal..." After you recognized the increased level of risk these conditions presented, you should have amended the informed consent document to inform potential subjects that these conditions could expose them to unacceptable risks if they participated in the study.
- B. You did not amend the informed consent document following the Grade III liver enzyme elevations experienced by each of the four subjects enrolled in the fourth dose cohort (Subjects _____). These were "significant" adverse events as defined in protocol section 4.1.6. Nevertheless, despite this important evidence of increased risk, you failed to provide potential subjects contacted after the fourth dose cohort with information about this possible risk of participation.
- C. You did not amend the informed consent document to inform potential subjects that (1) higher doses of vector were associated with disseminated intravascular coagulation (DIC) in animals, and (2) that the infusion of the viral vector might result in DIC for the human study subjects. Monkey AH4T was infused with the investigational vector in study #98-63 on October 27, 1998. Within two days the monkey developed symptoms of DIC. Two other monkeys that received different, but related vectors, were euthanized within five days of vector infusion due to severe DIC. Yet, you failed to amend the informed consent document to inform prospective subjects of the possibility of this potentially life-threatening adverse event, and you proceeded to infuse Subject _____ on November 17, 1998, and Subject _____ approximately four months later, without amending the consent form and obtaining approval by the IRBs.
- D. You did not amend the informed consent document to include the discomforts experienced by the subjects enrolled in the study. Significant periods of chills, nausea, and vomiting were experienced by most subjects, yet you did not inform prospective subjects that these symptoms were likely to occur. Prospective subjects for the later dose cohorts might

not have agreed to participate in the study if they had known that these symptoms were expected to occur. In addition, as the study progressed, subjects were routinely administered other medications in addition to acetaminophen to try to prevent the development of high fevers. The consent form states only that Tylenol would be administered.

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

Please notify us, in writing, within fifteen (15) business days after receipt of this letter, of the steps you have taken or will take to correct these violations and to prevent the recurrence of similar violations in future studies. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. This letter does not preclude the possibility of a corollary judicial proceeding or administrative action concerning these violations.

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

Please send your written response to:

Patricia Holobaugh (HFM-664)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
Telephone: (301) 827-6221

We request that you send a copy of your response to the Food and Drug Administration's Philadelphia District Office, U.S. Customhouse, 2nd and Chestnut Streets, Room 900, Philadelphia PA 19106.

Sincerely,



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

Page 9 - Dr. Batshaw

cc: Children's Hospital of Philadelphia IRB
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