



AUG 7 2002

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CBER – 02 -- 014

Warning Letter

N. Simon Tchekmedyan, M.D.
Pacific Shores Medical Group
1043 Elm Avenue, Suite 104
Long Beach, California 90813

Dear Dr. Tchekmedyan:

During the period from March 25 through April 5, 2002, Diane C. Van Leeuwen and Vien Q. Le, investigators with the Food and Drug Administration (FDA), reviewed your conduct of a clinical study entitled *Phase I Study of Anti-Tumor-Associated Glycoprotein 72 (TAG-72) Bispecific Antibody (MDX-220) in Patients with Advanced Adenocarcinomas Expressing TAG-72*. The inspection was conducted under the FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational drugs. A Form FDA 483, Inspectional Observations, was issued to you and discussed with you at the conclusion of the inspection.

We have reviewed your written response dated May 13, 2002, and addressed to Mr. Alonza Cruz, to the FDA Form 483. Although your letter provides a response to 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 in Title 21, Code of Federal Regulations (CFR) Parts 50 and 312 (available at <http://www.access.gpo.gov/nara/cfr/index.html>). The applicable provisions of the CFR are cited for each violation.

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

A. You did not follow the protocol for reporting serious adverse events. The protocol required that serious adverse events be reported to the sponsor within _____ followed by a written report within _____ working days. Written reports of grade 4 or fatal toxicities were required to be reported to the Institutional Review Board (IRB) within _____ working days. The following table summarizes serious adverse events that were not reported within the time frames established by the protocol.

Subject #	Serious Adverse Event	Date of Serious Adverse Event	Date Sponsor Notified	Date IRB Notified
# —	Cellulitis	09/24/98	*	Not notified
# —	Death	_____	10/27/98	02/06/02
# —	Death	_____	*	02/06/02
# —	Fluid Overload	10/15/98	*	Not notified
# — Event 1	Shortness of breath Grade 4	11/16/01	*	12/04/01
# — Event 2	Shortness of breath Grade 4	11/21/01	*	12/04/01
# — Event 3	Death	_____	*	12/4/01

* Serious adverse event report issued within protocol-required time frame

In your response letter you acknowledge that serious adverse events were not reported to the sponsor and/or the IRB in a timely manner for subjects # —, # —, and # — attributing the failures to report to administrative delay or administrative error. You state that you have implemented procedures for tracking and documenting adverse event reports in order to improve the accuracy and timeliness of your adverse event reporting in clinical trials.

As described in the table above, subject # — experienced Grade 4 shortness of breath on November 16, 2001 and November 21, 2001. Subject — died on _____. Although these events were timely reported to the sponsor, you did not notify the IRB of these three events until December 4, 2001. These failures to report were not specifically listed in the 483. We now request that you respond to them

B The protocol requires the administration of _____ of acetaminophen prior to infusion of the test article. You failed to follow the protocol by administering _____ of acetaminophen prior to infusion of the test article to the following subjects: #____ (before each of _____ infusions); #____ (before each of _____ infusions); #____ (before each of _____ infusions); and _____ and #____ before _____ infusion each) Subject #____ also received doses of _____, respectively, before each of _____ infusions.

Your response letter acknowledges the administration of _____ of acetaminophen instead of _____ prior to test article infusion

C. You failed to perform study evaluations required by the protocol

- i. Screening tests, specifically urinalysis, TAG-72, and Human Anti-Bispecific Antibody (HABA), were not completed for subject #____
- ii. The screening urinalysis test was not completed for subjects #____ and #____
- iii. Day 0 physical examination for subject #____ as not performed.
- iv. Day 0 and Day 14 vital signs were required to be monitored every _____ during infusion of study drug. Only one temperature was recorded for subject #____ during Day 0 infusion that was administered from 1045 to 1500.

Your response letter acknowledges these deviations

D You failed to conduct test procedures at intervals required by the protocol. The protocol requires screening tests be performed after the consent form is signed and within _____, prior to Day 0. The following tests were not performed within the timeframe required by the protocol:

Subject	Screening Test	Date consent signed	Date of Test	Day 0
#____	Chest X ray and CT scans	8/31/98	8/18/98	9/8/98
#____	ECG	4/27/00	4/13/00	5/11/00
#____	CT scans	5/2/00	4/24/00	5/11/00
#____	ECG	3/21/00	3/21/00	5/31/00

Your response letter acknowledges these deviations.

E. You failed to record all data on the Case Report Forms (CRF) as specified by the protocol

i. The following abnormal laboratory values were not recorded as adverse experiences on the Adverse Experience Case Report Forms as required by the protocol:

Subject #	Test	Study Day	Result	Grade
#	Hemoglobin	Day 0	7.3 g/dL	3
#	Total Bilirubin	Day 10	15.7 mg/dL	4
#	Glucose	Day 10	414 mg/dL	3

Your response letter acknowledges these deviations

ii. The following adverse events were not recorded on the Adverse Experience Case Report Forms as required by the protocol

Subject #	Event
#	Depression on 7/23/98, 7/24/98, and 7/25/98
#	Emesis on 7/15/98
#	Depression 8/14/98-8/24/98
#	Decrease L4-L5 sensory distribution and complaints of radiating hip pain with numbness
#	Multiple episodes of emesis, anorexia, severe nausea, and severe fatigue
#	Deep tendon reflexes 5/22/00

Your response letter acknowledges these deviations.

iii. The following concomitant medications were not recorded on the Concomitant Medication Case Report Form as required by the protocol:

- a. Ciprofloxacin for subject # for urinary tract infection on 6/20/98
- b. Lactulose, Kytril, and Zofran for subject # prior to treatment with the study drug.
- c. Robitussin with Codeine for subject # on 2/26/01

Your response letter acknowledges these deviations

2. 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)].

- A. The Case Report Form states that flow cytometry and cytokine tests were performed for Subject #— on 11/16/01, but the subject's case history does not report the results of these tests which are pertinent to the investigation and required by the protocol.

Your response letter states that flow cytometry and cytokine testing were no longer being performed. You included a facsimile transmission stating that flow cytometry and cytokine testing should end, yet the protocol required that the tests be performed and the Case Report Form says they were performed when they were not →→. Please explain why the Case Report Form states that these tests were performed yet there are no test results showing that the tests were performed.

- B. We note that you failed to retain the IRB approved protocol that was in effect when you enrolled subjects # ———. While you showed the FDA investigators another sponsor's policy that requires that an outdated protocol version be destroyed when superceded, that policy was not in effect for this particular protocol. You must retain these superceded protocol versions for the period of time required by 21 CFR 312.62(c). In your response letter, you state that you will keep older protocol versions in the study binder clearly identified as "no longer applicable."

Your response letter describes procedures you have implemented to improve the completeness, accuracy, and timeliness of your adverse event reporting. You also have instituted procedures to re-verify that all eligibility criteria are met and that no exclusion criteria are present before drug protocol therapy or intervention is started.

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 and to protect the rights, safety, and welfare of subjects under your care.

Please respond to the items designated by "→→" in writing within fifteen (15) business days of receipt of this letter. Your response should include any documentation necessary to show that correction has been achieved.

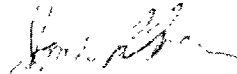
This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that the failure to effectively put into practice the corrective actions you have described in your response letter, and/or the commission of other violations may result in the initiation of enforcement action(s) 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

Christine Drabick
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
Telephone: (301) 827-6221

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: Alonza E. Cruse, Director
Food and Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612-2445

Institutional Review Board

