DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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CERTIFIED MAIL - RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

Stanislaw R. Burzynski, M.D., Ph.D.
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Dear Dr. Burzynski:

Between August 6 and 10, 2001, Messrs. Joel Martinez, Patrick Stone and Dr. Khin Maung U, representing the Food and Drug Administration (FDA), met with you and your staff to review: 1) your conduct as sponsor/investigator of clinical studies ([redacted] active protocols) of the investigational drug Antineoplaston A 10 and Antineoplaston AS2-1; and 2) your records that you maintain as the sponsor/investigator of those studies. This inspection was a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

This inspection was initiated to evaluate the [redacted] active protocols known to FDA under IND (b) (4) and IND (b) (4) Of approximately (b) (4) subjects enrolled under these INDs, either in protocols or as Special Exceptions, the FDA audit and evaluation of radiological films in this inspection were focused on the records of [redacted] subjects reported by you as having obtained a "complete response" or a "partial response." Although the records of the approximately (b) (4) subjects reported by you as "non-responders" were not reviewed in their entirety, selected records were inspected for compliance with FDA regulations. During the inspection, the FDA investigators were joined by Drs. Stephen I. Hirschfeld, Larry E. Kun, James M. Provenzale and Sarah A. Taylor who reviewed the radiological materials of the subjects you claimed as responders. The rationale for examining the records of these subjects you claimed as responders was to assess the credibility of the studies as reported to FDA in the annual reports, to assess the potential risks and benefits for subjects who may enroll in these studies, and to assess adherence to standards of good clinical practice.

We note that at the conclusion of the inspection, our personnel presented and discussed with you and your staff the items listed on Form FDA 483, Inspectional Observations. We acknowledge your August 23, 2001. response to the Form FDA 483 addressed to Mr. Michael E. Chappell of the FDA Dallas District Office in Dallas, Texas.

Although we accept some of the explanations provided in your August 23, 2001, response, we conclude that you failed to meet certain regulatory obligations as the sponsor/investigator in the conduct of your studies.

1. Federal regulations require that you report serious adverse events to the FDA within 15 days. You failed to report serious adverse events that are reflected in Burzynski Research Institute (BRI) records for the following subjects:

PROTOCOL #	SUBJECT ID	DATE	SERIOUS AND UNEXPECTED ADVERSE EVENTS
BT-07	[redacted] BT-07 [redacted]	31-Oct-2000	Became lethargic, with diarrhea and blood in the urine, and was hospitalized during which significant hematuria persisted.
		04-Dec-2000	Cystoscopy showed severe hemorrhagic cystitis and necrotic bladder mucosa.
BT-08	[redacted] BT-08 [redacted]	14-Aug-2000	Shortness of breath; chest X-ray showed suspicious consolidations in right lung base.
		20-Aug-2000	Hospitalized, bronchoscopy and lavage revealed *Pneumocystic carinii*.
BT-11	[redacted] -BT-11 [redacted]	02-Feb-1997	Pancreatitis; antineoplastons were discontinued for one week and pancreatitis improved. Antineoplastons restarted on 28-Feb-1997.
			Developed pancreatitis again and required antineoplastons to be discontinued permanently on 10-Mar-1997.
BT-15	[redacted] BT-15 [redacted]	30-Sep-1999	Hospitalized with fever, pneumonia and sepsis, and the clinical condition deteriorated, requiring transfer to ICU. Died on 17-Oct-1999.
BT-21	[redacted] -BT-21 [redacted]	03-Aug-1998	Subject developed aspiration pneumonia in hospital.
BT-22	[redacted] -BT-22 [redacted]	13-Sep-1999	Renal tubular acidosis requiring daily treatment with sodium bicarbonate.
		11-22 Nov-1999	Diarrhea with stool cultures positive for *Clostridium difficile* for which the subject was treated with Vancomycin
LY-06	[redacted] LY-06 [redacted]	22-Sep-1999	Lung biopsy revealed fibrosis of lung for which the subject was hospitalized and required oxygen. Died on 01-Oct-1999.
UP-02	[redacted] UP-02 [redacted]	03-Jul-1998	Hospitalized for septic shock (fever, hypotension), was intubated and placed on ventilator the next morning, and died at noon on 04-Jul-1998.

In your written response, you stated in a general manner that it was your "understanding that it was necessary to report to FDA only such adverse events which are possibly, probably and definitely related to the study drugs," and that you were "reporting such adverse events monthly and serious adverse events within 3 days."

Of major concern is the finding that serious adverse events that required hospitalization of subjects, and severe life-threatening adverse events such as pancreatitis that were not reported and were not recorded in the case report forms (CRFs) reviewed by FDA. These serious life-threatening adverse events were found only during the inspection while reviewing the medical progress notes for certain subjects.

For example, and of particular note, in the case of subject [redacted] BT-11 [redacted] abdominal pain with elevated lipase and amylase consistent with pancreatitis was observed; antineoplastons were discontinued for one week and restarted on 28-Feb-1997 after which the subject again developed pancreatitis. Pancreatitis appeared when the subject was challenged and re-challenged with antineoplastons, which suggests that this event was definitely related to antineoplastons. You discontinued antineoplastons permanently on 10-Mar-1997, which implies that you, yourself, believed that the pancreatitis was related to the administration of antineoplastons. Despite this history, you did not report this subject's pancreatitis to FDA at any time.

2. Federal regulations require that you submit a summary of all IND safety reports in the Annual Report. You failed to report adverse events associated with central venous line placement that are reflected in BRI records for the following subjects:

PROTOCOL #	SUBJECT ID	DATE	SERIOUS AND UNEXPECTED ADVERSE EVENTS
BT-08	[redacted]BT-08[redacted]	17-Jun-2000	Left subclavian vein thrombosis at the infusion site
BT-11	[redacted]BT-11[redacted]	18-May-2000	Central line sepsis (blood culture positive for *Staphylococcus aureus*) requiring hospitalization.
		20-May-2000	Broviac catheter was removed by surgery
BT-22	[redacted]BT-22[redacted]	29-Oct-1999	Central line sepsis, blood culture grew coagulase negative *Staphylococcus* that required treatment with Vancomycin.
LY-08	[redacted]LY-08[redacted]	11-Aug-1997	Occlusion of both subclavian veins at the infusion sites.

3. You failed to maintain adequate and accurate records in that:

   a. Discrepancies were noted between the CRFs and the respective source documents (specifically, medical charts and progress notes) for the following subjects:

PROTOCOL #	SUBJECT ID	INFORMATION ON CRF	INFORMATION ON SOURCE DOCUMENT
BT-13	[redacted]BT-13[redacted]	Withdrawn 09-Oct 1999.	Continued on study until 09-Nov-1999
BT-17	[redacted]BT-17[redacted]	Withdrawn on 27-Nov-1996, Reason = Patient's request	Withdrawn on 5-Dec-1996 with MRI findings (18-Jun-1996 vs 30-Sep-1996) suggestive of recurrent tumor.
BT-20	[redacted]BT-20[redacted]	Withdrawn on 30-Jul-1996. Reason = Patient's request	Hospitalized on 30-Jul-1996 with grand mal seizures and antineoplaston dose was reduced. Then, the patient decided to stop antineoplastons permanently.
BT-22	[redacted]BT-22[redacted]	Withdrawn on 27-Nov-1999; Reason = Worsening of clinical condition	Died the morning of 27-Nov-1999.
LY-06	[redacted]LY-06[redacted]	Withdrawn on 29-Dec-1999, Reason = Patient's request	On 28-Dec-1999, the abdominal CT of 23-Nov-1999 was reported with splenomegaly; recommended on 29-Dec-1999 to undergo splenectomy and stop antineoplaston treatment.
[redacted]	[redacted]LY-08[redacted]	Died on 27-Nov-1997.	Died on 27-Dec-1997.
UP-02	[redacted]-UP-02[redacted]	Withdrawn on 04-Jul-1998, Reason = Worsening of clinical condition	Hospitalized in ICU on 03-Jul-1998 for bacterial sepsis, and died on 04-Jul-1998.

For [redacted]BT-13[redacted] you stated in your August 23, 2001 response that you found "an error in information on CRF which was already corrected", and that you "are in the process of auditing" your "CRFs and entire medical records" and that during this process you "are occasionally finding errors which are immediately corrected". Notwithstanding your explanation, your responsibility for maintaining adequate and accurate records includes ensuring that there are not discrepancies between the CRFs and the medical records/source documents. Making corrections to the CRFs as much as two years after the fact is not sufficient to meet your responsibility in maintaining adequate and accurate records.

For subject [redacted]BT-17[redacted] you stated in your August 23, 2001 response that "[a]fter careful checking we found that there is no discrepancy between information on CRF and information on source document." However, this subject was recorded in the CRF as having

been withdrawn based on "patient's request". Treatment failure necessitated withdrawal of the subject from the study, independent of the subject's desire to withdraw. The CRF did not document that the subject withdrew because of MRI findings suggestive of recurrent tumor.

For subject (b) (7)(C) -BT-20- (b) (4) you stated in your August 23, 2001 response that you "found information in the CRF and in source document" that "indicates that the patient decided to discontinue administration of antineoplastons (patient's request)." However, the information that the subject was hospitalized on 30-Jul-1996 with grand mal seizures and that the antineoplaston dose had to be reduced, and subsequently, the subject decided to stop taking antineoplaston permanently, was not documented in the CRFs.

For subject (b) (7)(C) LY-06- (b) (4) you stated in your August 23, 2001 response that "[t]he patient was advised to consider splenectomy because of the difficulty swallowing a sufficient dose of Antineoplaston A10 and AS2-1 capsules," and that "[s]ince she had other organs involved with lymphoma, it was our advice to restart antineoplastons after splenectomy. Withdrawal from the study was based on the patient's decision (patient's request)." However, the information that the subject was recommended to undergo splenectomy on 29-Dec-1999 and therefore to stop antineoplastons was not documented in the CRFs.

For subjects (b) (7)(C) -BT-22- (b) (4) and (b) (7)(C) -UP-02- (b) (4) who died on the day they were withdrawn from the study but were recorded in the CRFs as withdrawn because of worsening of clinical condition, you stated in your August 23, 2001, response that "in the CRF under 'Revisions' the reason for withdrawal is corrected on 2/21/01 to death." Making corrections to CRFs more than a year after the fact is not sufficient to meet your responsibility to maintain adequate and accurate records.

For subject (b) (7)(C) LY-08- (b) (4) you stated in your August 23, 2001 response that "the patient's date of death was confirmed (by checking the Social Security Death Index) as November 27, 1997." However, the source document recorded the wrong month of death as December 27, 1997.

b. The CRFs do not always contain complete and accurate information in that the CRFs for subjects (b) (7)(C) -BT-23- (b) (4) , (b) (7)(C) -BT-23- (b) (4) and (b) (7)(C) -BT-09- (b) (4) do not contain entries regarding inclusion/exclusion criteria.

You stated in your August 23, 2001 response that "The entries for inclusion/exclusion criteria have been added to case report forms for these patients." Inclusion/exclusion criteria must be recorded at the time the subject was enrolled into the study; it is not acceptable to add these inclusion/exclusion criteria to the CRFs well after enrollment. Even if relevant information is available in the source documents, it is unlikely that complete information regarding inclusion/exclusion criteria will be available in the source documents.

4. You failed to conduct the clinical studies in accordance with the approved protocols in that:

   a. The following subjects who had prior chemotherapy and/or radiation therapy received antineoplaston treatment after a shorter interval than is specified in the protocol:

PROTOCOL #	SUBJECT ID	PRIOR THERAPY	LAST DATE OF PRIOR THERAPY	DATE ANTINEOPLASTONS STARTED	PROTOCOL-SPECIFIED INTERVAL (WEEKS)
BT-11	[redacted]-BT-11[redacted]	Etoposide	(b) (4)	24-Apr-1998	(b) (4)
BT-22	[redacted]BT-22[redacted]	Stereotactic radiation		10-Nov-1999	
BT-22	[redacted]BT-22[redacted]	Etoposide		30-Apr-1999	
PA-02	[redacted]PA-02[redacted]	Combined Chemotherapy (b) (4) and Radiation	(b) (4)	05-Aug-1999	

   In your August 23, 2001 response, you stated that for subject (b) (7)(C) BT-11 (b) (4), the (b) (4) of the head after completion of chemotherapy revealed an increase of tumor size and that FDA allows such subjects to be admitted prior to the protocol-specified interval. FDA may grant exceptions to a protocol on a case by case basis; however, you did not obtain an exception from FDA to treat this subject before the protocol-specified interval had elapsed.

   For subjects (b) (7)(C) BT-22 (b) (4) and (b) (7)(C) BT-22 (b) (4) who were in the BT-22 protocol, you stated in your August 23, 2001 response that these were "patients who (b) (4) (b) (4) or (b) (4) (b) (4) and (b) (4)" However, you did not obtain an exception from FDA to enroll these subjects prior to the end of the protocol-specified intervals.

   You stated in your August 23, 2001 response that subject [redacted] PA-02 (b) (4) "developed progressive and worsening of his condition" and "became wheelchair bound" which was why you "decided to admit him 5 days sooner than (b) (4) (b) (4)" You attached a copy of FDA correspondence in which you claimed that you "were informed that acceptance of the patient prior to the protocol's specified interval is only a minor violation" and that you "were advised to accept the patient to the study." However, the copy of FDA correspondence attached with your response is not for subject [redacted] PA-02 (b) (4) (a male) but for a female subject.

   b. Subject (b) (7)(C) BT-07 (b) (4) received traditional radiation therapy while participating in the clinical trial, which is prohibited by the protocol.

   You stated in your August 23, 2001 written response that this subject "who was away from Houston under the care of her local physician underwent radiation treatment to the brain without [your] approval and without [your] knowledge," and that you "were notified about her radiation therapy *after* she already received such treatment" (emphasis added). This was also documented in your progress notes dated 11-Mar-1998. However, the medical records

inspected on-site contained a fax from the subject's husband to BRI dated 13-Jan-1998 informing you that the subject's physician recommended radiation. The medical records inspected on-site also contained a Radiation Oncology Consultation Report dated 07-Jan-1998 by (b) (4) of (b) (4) (b) (4) Both of these documents indicate you were aware, prior to its occurrence, that the subject was going to receive traditional radiation therapy while on the study.

5. You failed to maintain adequate drug accountability records in that BRI receipt records for Lot 199 (AS2-1 500 ml bags) show that (b) (4) bags were received, but drug accountability records account for only (b) (4) bags.

   In your response dated August 23, 2001, you provided corrected drug accountability records for Lot 199 (AS2-1 500-ml bags). However, this only accounted for (b) (4) bags; your corrected drug accountability records do not account for the total of (b) (4) bags that were received according to BRI receipt records.

6. You failed to update the consent form regarding the significant new findings that developed during the course of the research that may have affected the subject's willingness to participate in the study. Although the Division of Oncology Drug Products granted special exception treatment IND (b) (4) dated 8-28-97 for subject (b) (7)(C) LY-07 (b) (4) the exception was conditioned on the incorporation of the following statements:

   a. An awareness to the patient that protocol (b) (4) is intended to measure response;
   b. To date there have been no responses from [redacted] patients on this protocol;
   c. No responses in [redacted] patients on Special Exception; and
   d. There is no way to know if receiving antineoplastons will be of any benefit to this patient.

   In your response dated August 23, 2001, you admitted that you "do not have any explanation as to why this statement was not included except for human error."

Because of the departures from FDA regulations discussed above, we request that you inform this office, in writing, within thirty (30) working days from the date of receipt of this letter, of the actions you have taken or plan to take to bring your procedures into compliance with FDA regulations and to ensure that the violations are not repeated in any ongoing or future studies.

We wish to remind you that, as the sponsor/investigator, you are responsible for ensuring: adherence to federal regulations; proper monitoring of the investigations; the investigations are conducted in accordance with the general investigational plan and protocols; and adequate adverse event reporting.

We plan to monitor your research activities to ensure that you have, indeed, implemented appropriate actions to correct the violations noted and that your revised clinical investigational practices comply with federal regulations.

We appreciate the cooperation shown our personnel during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice I, by letter at the address given below.

Sincerely yours,

Antoine El-Hage

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