Dear Dr. Burzynski:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between January 7, 2013, and March 15, 2013. Mr. Joel Martinez, Mr. Hugh McClure, and Dr. Cynthia Kleppinger, representing the FDA, reviewed your conduct of the following clinical investigations of the investigational drugs Antineoplastons A10 and AS2, performed for Burzynski Research Institute, as well as your expanded access use of the investigational drugs Antineoplastons A10 and AS2:

- Protocol BT-09, "Phase II Study of Antineoplastons A10 and AS2-1 in Patients with Brain Tumors";
- Protocol BT-10, "Phase II Study of Antineoplastons A10 and AS2-1 in Children with Brain Tumors";
- Protocol BT-21, "Phase II Study of Antineoplastons A10 and AS2-1 in Adults with Primary Malignant Brain Tumors";
- Protocol BT-22, "Phase II Study of Antineoplastons A10 and AS2-1 in Children with Primary Malignant Brain Tumors"; and
- Protocol AD-02, "Phase II Study of Antineoplastons A10 and AS2-1 in Patients with Carcinoma of the Adrenal Gland."

This inspection is a part of FDA’s Bioresearch Monitoring Program, which includes inspections
designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Mr. Martinez, Mr. McClure, and Dr. Kleppinger presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your April 5, 2013, written response to the Form FDA 483. We also acknowledge receipt of a progress update from you, dated May 15, 2013, regarding your response to the Form FDA 483.

From our review of the FDA establishment inspection report, the documents submitted with that report, and your April 5, 2013, written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

1. **You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].**

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plans. The investigational plans for Protocols BT-09, BT-10, and BT-21 require that you assign therapeutic responses based on how the subjects’ tumors respond to the study drug, and that you report adverse events to the sponsor. Correct assignment of therapeutic responses is important to determine the extent, if any, to which the tumors respond to the study drug. Reporting of adverse events is important to minimize risk to subjects and to ensure that the sponsor has complete and accurate data regarding the safety of the study drug. You failed to ensure that Protocols BT-09, BT-10, and BT-21 were conducted according to the investigational plans. Specifically:

   a. Protocols BT-09, BT-10, and BT-21 define each possible therapeutic response (Complete Response, Partial Response, Stable Disease, and Progressive Disease), and include specific criteria you must use to classify a subject as having one of those responses. You assigned therapeutic responses incorrectly for 9 of the 27 subjects whose therapeutic response classifications were reviewed during the inspection. Specifically:

   i. For a classification of Complete Response, Protocols BT-09, BT-10, and BT-21 required: (1) complete disappearance of all contrast-enhancing tumor on neuroimaging studies, and ancillary radiographic studies if appropriate, for a minimum duration of four weeks; and (2) that the subject be off corticosteroids.

   You incorrectly classified the following subjects as having a Complete Response:

   1. Protocol BT-10: Subjects 006389 and 013660 did not have complete disappearance of all contrast-enhancing tumor for at least four weeks and, therefore, were incorrectly classified as having a Complete Response.

   a. For Subject 006389, both the Tumor Measurements Case Report Form (CRF) and the list that you provided us of subjects enrolled in Protocol BT-10 as of January 7, 2013, identify this subject as having a Complete Response. However, the Tumor Measurements CRF shows that none of the neuroimaging studies showed complete disappearance of contrast-enhancing tumor for at least four weeks. Therefore, the subject did not meet the criteria for Complete Response.

   b. For Subject 013660, both the Tumor Measurements CRF and the list that you provided us of subjects enrolled in Protocol BT-10 as of January 7, 2013, identify this subject as having a Complete Response. However, the Tumor Measurements CRF shows that none of the neuroimaging studies showed complete disappearance of contrast-enhancing tumor for at least four weeks. Therefore, the subject did not meet the criteria for Complete Response.
2. Protocol BT-09: For Subject 007197, the Tumor Measurements CRF indicates, based on Magnetic Resonance Imaging (MRI) taken on July 25, 2001; September 11, 2001; and November 8, 2001, complete disappearance of all contrast-enhancing tumor for a minimum duration of four weeks. However, the Steroids Report CRF and the Oncology-Hematology Flow Sheet show that the subject was on corticosteroids preceding the July 25, 2001 and September 11, 2001 MRIs; during the period between these MRIs; and up to one week prior to the November 8, 2001 MRI. Therefore, the subject did not meet the criteria for Complete Response.

3. Protocol BT-21: For Subject 009990, the Tumor Measurements CRF shows that the subject was classified as having a Complete Response based on Positron Emission Tomography (PET) scan results. However, the Steroids Report CRF shows that the subject was on corticosteroids preceding all of the relevant PET scan dates (January 4, February 4, June 14, and August 16, 2005), as well as during the period between these PET scans. Therefore, the subject did not meet the criteria for Complete Response.

ii. For a classification of Partial Response, Protocol BT-09 required: (1) that subjects have more than 50% reduction in the sum of the products of the greatest perpendicular diameters of contrast-enhancing tumors, compared to the corresponding baseline evaluation, for at least four weeks; (2) that no simultaneous increase in size of any lesion or the appearance of new lesions may occur; and (3) that subjects be on a stable or decreasing dose of corticosteroids.

You incorrectly classified Subject 008765 as having a Partial Response. For Subject 008765, the Tumor Measurements CRF shows that the subject was classified as having a Partial Response based on a radiology report dated May 1, 2003. Although the May 1, 2003 radiology report shows a tumor reduction of greater than 50%, there are no MRIs between November 1, 2002 (baseline MRI) and the May 1, 2003 radiology report that show that the tumor reduction of greater than 50% was maintained for at least four weeks during that time period. Further, the April 29, 2003 radiology report (for the April 21, 2003 MRI) actually shows an increase in tumor size. Therefore, the subject did not meet the criteria for Partial Response.

iii. For a classification of Stable Disease, Protocol BT-10 required: (1) that subjects have less than 50% change (either greater or smaller) in the sum of the products of the perpendicular diameters of the enhancing tumor compared to the baseline evaluation; (2) that this state be maintained for a minimum of 12 weeks; and (3) that the corticosteroid dose is stable or decreasing.

You incorrectly classified the following subjects as having Stable Disease:

1. Protocol BT-10: Subjects 012184, 012206, and 012252 were not on stable or decreasing dose of corticosteroids and, therefore, were incorrectly classified as having Stable Disease. Subject 011373 did not have a less than 50% change in tumor size maintained for at least 12 weeks and was not on either a stable or decreasing dose of corticosteroids and, therefore, did not meet the criteria for Stable Disease.

a. For Subject 012184, the Tumor Measurements CRF indicates, based on MRIs taken on January 7, April 20, June 18, and July 24, 2009, that the subject had a less than 50% change in tumor size compared to baseline, and that this state was maintained for a minimum of 12 weeks. However, the Steroids Report CRF shows that the subject was not on either a stable or decreasing dose of corticosteroids. Therefore, the subject did not meet the criteria for Stable Disease.

b. For Subject 012206, the Tumor Measurements CRF indicates, based on MRIs taken on January 15 and May 6, 2009, that the subject had a less than 50% change in tumor size compared to baseline, and that this state was maintained for a minimum of 12 weeks. However, the Steroids Report CRF shows that the subject was not on either a stable or decreasing dose of corticosteroids. Therefore, the subject did not meet the criteria for Stable Disease.

c. For Subject 012252, the Tumor Measurements CRF indicates, based on MRIs taken on April 21
and August 7, 2009, that the subject had a less than 50% change in tumor size compared to baseline, and that this state was maintained for a minimum of 12 weeks. However, the Steroids Report CRF shows that the subject was not on either a stable or decreasing dose of corticosteroids. Therefore, the subject did not meet the criteria for Stable Disease.

d. For Subject 011373, the Tumor Measurements CRF shows that the subject did not have a less than 50% change in tumor size, compared to baseline, maintained for at least 12 weeks. In addition the Steroids Report CRF shows that the subject was not on either a stable or decreasing dose of corticosteroids.

The Tumor Measurements CRF shows that Subject 011373 had a baseline MRI taken on April 12, 2007. The subject began receiving investigational drug on April 13, 2007, and had additional MRIs taken on May 18, July 6, and July 19, 2007. The Tumor Measurements CRF documents that a change of less than 50% in tumor size, compared to baseline, was maintained from May 18 through July 19, 2007; however, there are no confirmatory MRIs or PET scans after July 19, 2007, and there is therefore no evidence that the reduction was maintained for a minimum of 12 weeks. In addition, the Steroids Report CRF shows that the subject was not on either a stable or decreasing dose of corticosteroids. Therefore, the subject did not meet the criteria for Stable Disease.

In your April 5, 2013 written response to the findings noted above, you stated that “[t]he definition of a ‘patient off corticosteroids’ that we follow is one who continues on the lowest dosage necessary for neurologic stability and is maintained at their level of comfort and function.” In your response, you also cited the Neuro-Oncology Working Group recommendations that complete and partial responses can be determined when a patient is on physiologic replacement doses of corticosteroids. Further, you indicated that draft amendments for Protocols BT-09, BT-10, and BT-21 have been prepared by the sponsor for submission to the Institutional Review Board (IRB), to “correct the practical interpretation of ‘off steroids’ as currently specified in our protocols,” and you stated that the sponsor will amend the protocols to concur with the original intent of allowing steroids.

In addition, you indicated in your written response that you are retaining the original assessments of Complete Response, Partial Response, and Stable Disease (as applicable) for Subjects 013660, 009990, 008765, 012184, 012206, 012252, and 011373 listed above. You indicated that, with the exception of Subjects 009990 and 011373, you are maintaining the original assessment for all of these subjects based on the sponsor’s proposed changes to the tumor assessment criteria, that is, not based on the tumor assessment criteria as included in the protocols at the time the relevant subjects were evaluated. For Subject 009990, you indicated that you were maintaining the assessment as a Complete Response based on the sponsor’s proposed changes to the tumor assessment criteria and based on central radiology review, which suggested a Complete Response metabolically. For Subject 011373, you indicated that two consecutive MRIs of the subject using enhancement were unavailable, and that the subject was classified as having Stable Disease based upon the nonenhancement portion of the tumor for the corresponding MRIs.

Your responses noted in the preceding paragraphs are inadequate. The protocols required specific consideration of corticosteroid use. In addition, the definition of “a patient off corticosteroids” that you stated you followed, was not included in any of the protocols listed above.

We acknowledge that the use of corticosteroids to maintain physiologic levels may be appropriate, despite protocol wording requiring that subjects be off corticosteroids completely for a Complete Response. However, for all of the subjects listed above as having been classified as a Complete Response despite being on corticosteroids, their corticosteroid doses were well beyond those needed to maintain physiologic levels. Specifically, these subjects were on doses of Decadron (dexamethasone, a corticosteroid) that ranged from 4 mg/day to 16 mg/day, while the physiologic-replacement equivalent of Decadron is in the range of 0.25 mg/day to 0.75 mg/day.

Also, the protocols’ requirement that a subject be “off corticosteroids” applies only to the Complete
Response assessment. Your written response does not address your incorrect classifications of Stable Disease in cases where subjects were not on stable or decreasing doses of corticosteroids. Further, your written response does not address the incorrect classification of Stable Disease that resulted from lack of a 12-week maintenance period for Subject 011373, as described above. Lastly, your written response is inadequate because you have not included a commitment to correct the study records that contain these incorrect response classifications. Please note that all corrections to study records must be done in accordance with the requirements of 21 CFR 312.62(b) and (c) to maintain and retain adequate and accurate case histories.

Failure to assess tumor response in accordance with the protocol requirements jeopardizes subject safety and welfare and raises concern about the validity and integrity of the data collected at your site.

b. Protocol BT-10 requires the clinical investigator to report any adverse events to the sponsor. You failed to adhere to this requirement. Specifically, Subject 023612 experienced adverse events, noted in Table 1, that were not reported to the sponsor.

Table 1. Adverse Events for Subject 023612 Not Reported to the Sponsor

<table>
<thead>
<tr>
<th>Date of Adverse Event</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 21, 2012</td>
<td>Rash at surgical site</td>
</tr>
<tr>
<td>August 6, 2012</td>
<td>Fever</td>
</tr>
<tr>
<td>August 10, 2012</td>
<td>Weakness and fatigue</td>
</tr>
<tr>
<td>August 28, 2012</td>
<td>Nausea, fatigue, and dizziness</td>
</tr>
<tr>
<td>September 14, 2012</td>
<td>Arthralgias</td>
</tr>
<tr>
<td>September 22, 2012</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>November 27, 2012</td>
<td>Right-ankle sprain</td>
</tr>
</tbody>
</table>

In your April 5, 2013 written response, you acknowledged that you did not report the adverse events listed above to the sponsor and stated, “Corrective action has been undertaken with staff.”

Your written response is not adequate because you have not provided details regarding the corrective action, to enable us to determine whether that corrective action appears adequate to prevent similar violations from occurring in the future.

2. You failed to protect the rights, safety, and welfare of subjects under your care [21 Cfr 312.60 and 21 CFR 312.305(c)(1)].

As a clinical investigator, you are required to protect the rights, safety, and welfare of subjects and expanded access patients under your care. This requirement includes, among other things, the responsibility to take adequate precautions to ensure that subjects and expanded access patients are not overdosed with the investigational drug. You failed to protect the safety and welfare of subjects and expanded access patients under your care by failing to take adequate precautions to ensure that these individuals were not overdosed. Examples of your failure include but are not limited to the following:

Study records documenting Antineoplaston overdoses show that expanded access patients and subjects in Protocols BT-09, BT-10, and AD-02 had overdoses. Of those subjects and expanded access patients identified in study records as having experienced overdoses, the following individuals experienced multiple overdoses:

a. Protocol BT-10: Subjects 012184, 013660, and 021539, and Expanded Access Patient 01981:
   i. Subject 012184 was overdosed on January 18 and February 26, 2009.
   ii. Subject 013660 was overdosed on April 25 and July 19, 2010.
iii. Subject 021539 was overdosed on July 12 and October 29, 2012.
iv. Patient 019813 was overdosed on April 5, April 30, and May 5, 2011, and on February 19, 2012.

b. Protocol AD-02: Subject 008809 was overdosed on December 13, 2006, and on October 5, 2008.

We recognize that with the exception of Patient 019813, the specific subjects listed above were not included in the related sub-part of the Form FDA 483 that you received and, therefore, your written response did not address the specific instances noted above. However, the Form FDA 483 did include Patient 019813, as well as other examples of overdoses, and you addressed those examples in your written response.

Specifically, in your April 5, 2013 written response, you state, “Overdose reports and the training that ensues following each event are carefully followed-up upon [sic]...We reviewed the cases cited in the inspectional observations and ascertained that all the patients/caregivers were retrained following each event.” You also note that effective immediately, you are instituting the following:

· Additional reinforcement training of staff regarding antineoplaston administration and how to handle and document accidental overdosing in an expedited manner.

· Monthly contacts with all caregivers to reinforce the training.

Your written response noted above is not adequate. With respect to your statement that you ascertained that all patients/caregivers were retrained following each event, the fact that the individuals listed above experienced more than one overdose indicates that any retraining that was provided was not adequate to prevent repeat overdosing.

With respect to your planned action to institute additional reinforcement training of staff and monthly contacts with all caregivers to reinforce their training, you have not provided details to enable us to determine whether that training appears sufficient to prevent similar violations from occurring in the future.

Your failure to take adequate precautions to ensure that subjects and expanded access patients were not overdosed with investigational drug raises significant concerns about your protection of study subjects enrolled at your site in the studies mentioned above, as well as concerns about your protection of expanded access patients whom you treated with the investigational drugs Antineoplastons A10 and AS2.

3. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60, 21 CFR 50.25(b)(3), and 21 CFR 50.27(b)(1)].

As a clinical investigator, you are required to obtain informed consent in accordance with 21 CFR part 50. Except in limited circumstances not applicable here, informed consent requires the use of a written consent document that embodies the elements of informed consent required by 21 CFR 50.25. An investigator shall give either the subject or the subject's legally authorized representative an adequate opportunity to read the written consent document (including all required elements) before it is signed. You failed to obtain informed consent in accordance with 21 CFR part 50 because the informed consent documents that you used for Protocols BT-10 and BT-22 did not contain all of the required elements of informed consent.

Specifically, the informed consent forms did not contain a statement regarding any additional costs to the subject that may result from participating in the research, as required by 21 CFR 50.25(b)(3). Research subjects were presented with a billing agreement only after they had already consented to participate in clinical research.
In your April 5, 2013 written response to this observation, you acknowledged that “[a] treatment billing agreement is only presented to the patient... after the ICD is signed.” In addition, you stated that “[a]t times, days or weeks may elapse between signing the ICD and presenting the treatment billing agreement.” As a corrective action, you proposed amended wording to informed consent documents to address the lack of a statement regarding additional costs to the subject that may result from participating in the research.

Your proposed amended wording is not adequate because it focuses primarily on whether there is a charge for the investigational agent; contains only general statements regarding the possibility of additional costs; and puts the responsibility on the subject to inquire about any expected added costs, rather than providing the subject with specific additional costs that may result from participation in the research. In contrast, the treatment billing agreement identifies the specific additional costs the subject will be expected to pay as a result of participating in the research. The informed consent document itself must include the information about the additional costs to the subject that may result from his or her participation in the research.

Failure to provide subjects with information regarding any additional costs prior to obtaining informed consent denies subjects the opportunity to make an informed decision regarding their participation in the clinical investigation.

4. **You failed to adhere to requirements for all expanded access uses with respect to maintaining accurate case histories and retaining records in a manner consistent with 21 CFR 312.62 [21 CFR 312.305(c)(4) and 21 CFR 312.62(b) and (c)].**

As a clinical investigator, in all cases of expanded access, you are responsible for maintaining accurate case histories and retaining records in a manner consistent with the requirements of 21 CFR 312.62. The regulation at 21 CFR 312.62(b) requires that you maintain accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. The regulation at 21 CFR 312.62(c) requires that you retain records required to be maintained under 21 CFR part 312 for a period of two years following the date a marketing application is approved for 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 two years after the investigation is discontinued and FDA is notified.

You have failed to maintain and retain accurate case histories as required in all cases of expanded access. Specifically, you failed to maintain and retain accurate case histories for Patient 022387, whom you treated under a Single Patient Protocol (individual patient expanded access), also referred to as a Special Protocol Exception, to Protocol BT-10.

In response to a (b)(6), FDA’s Division of Oncology Products 2 (DOP 2) requested that the sponsor, Burzynski Research Institute (BRI), provide DOP 2 with copies of the records for Patient 022387.

On (b)(6), BRI provided DOP 2 with copies of the following records for Patient 022387:

- Case Report Form titled “Physical Exam – Baseline,” for physical examination conducted on (b)(6)
- Case Report Form titled “Baseline Visit – Prior Cancer Treatment History”
- Case Report Form titled “Baseline Visit – Pathology History”
- Case Report Form titled “Adverse Events”

The records BRI submitted to FDA on (b)(6), were not in the files that you provided regarding
Patient 022387 during the inspection. However, during the inspection, you provided other Case Report Forms for this patient, with the same titles and for the same visit date as noted above, but containing information that differed from that which BRI submitted to FDA. Notable differences are contained in the following tables.

(b)(6)

(b)(6)

(b)(6)

We recognize that the Form FDA 483 issued to you does not include this as an observation and, therefore, your written response did not address this issue.

Please explain why the Case Report Forms at your site for Patient 022387 differed from the Case Report Forms that Burzynski Research Institute submitted to FDA’s Division of Oncology Products 2.

Failure to maintain and retain accurate case histories raises concerns about subject safety and data integrity, as well as concerns about the adequacy of safeguards in place at your site to protect patients being treated under expanded access.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to address the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity, M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}
Thomas N. Moreno, M.S.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
THOMAS N MORENO
12/03/2013

1 A classification of Complete Response does not reflect whether the response continued beyond the point in time at which the therapeutic response classification was made. That is, it is possible that a subject who is correctly classified as having a Complete Response could have tumor return later.

2 We note that this is consistent with a previously treated subject, Subject 005297. The Tumor Measurements CRF for that subject indicates, based on MRIs taken on August 11, 1997, and October 2, 1997, complete disappearance of all contrast-enhancing tumor for a minimum duration of four weeks. However, the Steroids Report CRF and Oncology-Hematology Flow Sheet show that the subject was on corticosteroids preceding the August 11, 1997 MRI and during the period between August 11, 1997, and the October 2, 1997 MRI (including on October 2, 1997). Therefore, Subject 005297 did not meet the criteria for Complete Response. For Subject 005297, you indicated that you had requested a second independent radiology review to confirm the correct response, and stated that you would forward this information to FDA after receipt. We note that as of the date of this letter, FDA has not received this information from you.

3 We note that the question of whether subjects were appropriately classified as having Stable Disease under protocol-specific criteria is distinct from the question of whether FDA would accept data on Stable Disease rates as the basis of an efficacy claim.

4 We note that the examples cited above are consistent with two previously treated subjects from Protocol BT-10 and Protocol BT-22 (which had the same criteria as Protocol BT-10 regarding classification of Stable Disease). For Subject 005974 in Protocol BT-10, the Tumor Measurements CRF indicates, based on MRIs taken on January 12, 1999, and April 6, 1999, that the subject had less than 50% change in tumor size compared to baseline, and that this state was maintained for a minimum of 12 weeks. However, the Steroids Report CRF shows that the subject was not on either a stable or a decreasing dose of corticosteroids. Therefore, the subject did not meet the criteria for Stable Disease. In your April 5, 2013 written response, you stated that you were reclassifying Subject 005974 as Progressive Disease, based on the sponsor’s proposed changes to the tumor assessment criteria.

5 We note that Protocols BT-09, BT-10, and BT-21 are closed. Your written response also indicated that the sponsor has prepared draft amendments for Protocol BT-22 for submission to the IRB. BT-22 is also closed.

6 We note that in your April 5, 2013 written response, you also indicated that you are maintaining the original assessment of Complete Response for Subject 007197, based on the sponsor’s proposed changes to the tumor assessment criteria.
We note that, based on your April 5, 2013 written response, the informed consent forms used for Protocol BT-09 also did not contain this information, and subjects were only presented with a billing agreement after they had signed the informed consent forms.