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Inspections, Compliance, Enforcement, and Criminal Investigations

[REDACTED] 12/3/13



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Dec 3, 2013

WARNING LETTER

**CERTIFIED MAIL
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Ref: 13-HFD-45-11-0

[REDACTED]

Dear Dr. [REDACTED]

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at [REDACTED] between January 17 and March 15, 2013. Mr. Joel Martinez, Mr. Hugh McClure, and Dr. Cynthia Kleppinger, representing the FDA, reviewed BRI's conduct as the sponsor of the following clinical investigations of the investigational drugs Antineoplastons A10 and AS2-1:

- 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 the 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.

In your April 5, 2013, written response, you stated that BRI was planning to submit an update to FDA on or before May 15, 2013, and monthly reports thereafter until BRI's corrective actions are completed. 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 BRI 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. Failure to ensure proper monitoring of the investigations and failure to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 21 CFR 312.56(a)].

FDA regulations require that sponsors ensure proper monitoring of clinical investigations and ensure that their clinical investigators conduct the investigations in accordance with the protocols contained in the Investigational New Drug file (IND). Our investigation found that BRI failed to ensure proper monitoring of the studies referenced above and did not ensure that a clinical investigator conducted the investigations in accordance with the protocols contained in the IND. As a result of inadequate monitoring, BRI did not identify, and correct in a timely manner, a clinical investigator's incorrect classification of therapeutic responses and failure to obtain informed consent from subjects in accordance with FDA regulations. 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 the clinical investigator must use to classify a subject as having one of those responses. BRI monitoring failed to identify and correct the clinical investigator's incorrect classification of therapeutic responses for 9 of the 27 subjects whose therapeutic response classifications were reviewed during the inspection. Specifically:
 - i. For a classification of Complete Response¹, 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.

BRI monitoring failed to identify and correct the clinical investigator's incorrect classification of 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 tumors for at least four weeks and, therefore, were incorrectly classified by the clinical investigator as having a Complete Response.
 - a. For Subject 006389, both the Tumor Measurements Case Report Form (CRF) and the list that the clinical investigator 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 the clinical investigator 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 MRIs 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.²
3. Protocol BT-21: Subject 009990 was not off corticosteroids and, therefore, was incorrectly classified

by the clinical investigator as having a Complete Response.

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.

BRI monitoring failed to identify and correct the clinical investigator's incorrect classification of the following subject as having a Partial Response:

Subject 008765 was incorrectly classified by the clinical investigator 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 Disease³, 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.

BRI monitoring failed to identify and correct the clinical investigator's incorrect classification of the following subjects as having Stable Disease⁴:

1. Protocol BT-10: Subjects 012184, 012206 and 012252 were not on stable or decreasing doses of corticosteroids and, therefore, were incorrectly classified by the clinical investigator 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 20 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 a baseline MRI was 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.

BRI failed to ensure proper monitoring of these clinical investigations because BRI did not identify and correct the clinical investigator's incorrect assessments of therapeutic responses. As a result, BRI has failed to ensure that the clinical investigations were conducted in accordance with the investigational plan.

BRI's April 5, 2013 written response included a general section related to BRI's monitoring practices, as well as specific responses to each of the individual sub-parts listed on the Form FDA 483. This letter will discuss the BRI response to the individual sub-parts in the order they appear in the letter, and the general response at the end of this violation.

BRI's April 5, 2013 written response indicated that BRI was 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. BRI indicated that, with the exception of Subjects 009990 and 011373, the clinical investigator will be maintaining the original assessment for all of these subjects based on BRI's proposed changes to the tumor assessment criteria, that is, not based on the tumor assessment criteria as included in the protocol at the time the relevant subjects were evaluated. For Subject 009990, BRI indicated that the clinical investigator was maintaining the assessment as a Complete Response based on BRI's proposed changes to the tumor assessment criteria and based on central radiology review, which suggested a Complete Response metabolically. For Subject 011373, BRI 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.

In addition, the response stated that BRI's "definition of a 'patient off corticosteroids' is one who continues on the lowest dosage necessary for neurologic stability and is maintained at their level of comfort and function." In the response, BRI 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, the response stated that BRI will amend Protocols BT-09, BT-10, and BT-21 "[t]o correct the practical interpretation of 'off steroids' as currently specified in the protocols" and will submit the protocol amendments to the Institutional Review Board (IRB) for review and approval at its April 13, 2013 meeting⁵.

BRI's response related to monitoring the clinical investigator's therapeutic response assessments is inadequate. BRI's proposal to amend the protocols is not responsive to BRI's failure to monitor the conduct of the clinical investigations properly. BRI was required to ensure that the clinical investigator complied with the protocols as written, which required specific consideration of corticosteroid use when assessing therapeutic response. In addition, BRI's definition of "a patient off corticosteroids" 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. BRI's written response does not address how monitoring failed to detect the incorrect assessments of Stable Disease in cases where subjects were not on stable or decreasing doses of corticosteroids. Further, BRI's 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. In addition, BRI's written response is inadequate because it does not include a commitment to have the clinical investigator 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.

Lastly, BRI has not indicated whether it is planning to submit its proposed protocol amendments to FDA. The described protocol changes reflect a significant change in the design of the protocols. As a result BRI is required to submit the protocol changes to FDA for review [21 CFR 312.30(b)(1)(ii) and (2)(i)(a)].

b. BRI monitoring failed to identify and correct the clinical investigator's failure to obtain informed consent from subjects in accordance with the provisions of 21 CFR Parts 312.60, 50.25(b)(3), and 50.27(b)(1). The informed consent documents (ICDs) used by the clinical investigator 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. **6**

BRI's monitoring did not identify and correct the clinical investigator's failure to include all required elements of informed consent. Therefore, BRI failed to ensure proper monitoring of these clinical investigations. As a result of this failure, BRI has also failed to ensure that the clinical investigations were conducted in accordance with the investigational plan.

BRI's April 5, 2013 written response to this observation acknowledged that "[a] treatment billing agreement is only presented to the patient... after the ICD is signed." In addition, the response stated that "[a]t times days or weeks may elapse between signing the ICD and presenting the treatment billing agreement." As a corrective action, BRI 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.

BRI's response related to monitoring the clinical investigator's provision of informed consent is inadequate. The 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 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.

BRI's April 5, 2013 written response identified several corrective actions related to BRI's general monitoring practices. The response acknowledged that as of 2005, BRI ceased using the Study Monitoring Plan dated 23 April 2004, and that "[e]rroneously our revised monitoring practices were not formally acknowledged in the form of revised monitoring guidelines." The response contained several attachments, including, for example, the following new SOPs:

- Study Monitoring Guidelines (SOP 420)
- GCP Monitoring (SOP 421)
- Review and Approval of Site Regulatory Documents for Submission (SOP 410)
- Clinical Trial Material Management (SOP 430)
- Reporting and Processing Adverse and Serious Adverse Events (SOP 702)

In addition to the implementation of these new SOPs, BRI has committed to immediately reinstating the use of a dedicated monitor to review data and Good Clinical Practice (GCP) documentation according to the new SOPs.

These corrective actions related to BRI's general monitoring practices, if properly carried out, appear adequate to prevent the recurrence of similar violations in the future. However, the corrective actions related to the specific issues identified in Items 1.a. and 1.b., above, are inadequate and should be addressed in your response to this letter. In addition, the Informed Consent Checklist for BRI's SOP 410,

titled "Review and Approval of Site Regulatory Documents for Submission," only cites the informed consent requirements under 45 CFR part 46. As an initial matter, any clinical investigations conducted under BRI's IND are subject to the informed consent requirements in FDA's regulations, in addition to any applicable regulations in 45 CFR part 46. Please revise the Informed Consent Checklist (410A) and any other SOPs to reflect applicable FDA regulations. Further, we note that 45 CFR 46.408(c) includes a provision whereby an IRB may waive the requirement to obtain parental permission in a clinical investigation that includes children as subjects. There is no analogous provision in FDA's regulations in 21 CFR part 50, subpart D (Additional Safeguards for Children in Clinical Investigations). Therefore, an IRB is not permitted to waive the requirement to obtain parental permission in an FDA-regulated clinical investigation. Please revise the Informed Consent Checklist (410A) accordingly.

2. Failure to obtain from an investigator sufficient financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR part 54 [21 CFR 312.53(c)(4)].

FDA regulations require that sponsors of clinical investigations obtain sufficient financial information from investigators to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54 of FDA's regulations. BRI failed to obtain financial information for each of the 122 sub-investigators participating in Protocols BT-09, BT-10, BT-21, and BT-22. There was no financial information for 40 sub-investigators for BT-09; 34 sub-investigators for BT-10; 40 sub-investigators for BT-21; and 8 sub-investigators for BT-22. BRI's April 5, 2013 written response indicated that BRI considered it unnecessary to obtain financial disclosures from these sub-investigators (all of whom were subjects' or patients' local physicians) because there were no financial relationships to disclose. BRI stated, "...we believe that we have sufficient information about both clinic personnel and sub-investigators to be in compliance with 21 CFR part 54." BRI further indicated that as corrective action, when BRI files the New Drug Application (NDA), BRI will submit one Form FDA 3454, will check Box 1, will attach a list of all of the local physicians, and will submit a brief addendum describing the facts set forth in the written response.

BRI's written response is not adequate, because BRI's responsibilities as an applicant at the time of an NDA filing differ from BRI's responsibilities as a sponsor of a clinical investigation. As a sponsor, BRI is required to comply with all of the relevant requirements in 21 CFR part 312, including the requirement to obtain financial information in accordance with 21 CFR 312.53(c)(4). BRI must collect this information at the IND stage even if BRI believes that there are no financial relationships to disclose, and it must obtain the sub-investigators' commitments to update this information promptly if any relevant changes occur during the investigation and for one year following the completion of the investigation.

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 explain the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe that BRI has 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.
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Sincerely yours,
{See appended electronic signature page}
Thomas N. Moreno, M.S.
Acting Office Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

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/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, BRI indicated that it 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.
- 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 decreasing dose of corticosteroids. Therefore, the subject did not meet the criteria for Stable Disease. In BRI's April 5, 2013 written response, BRI stated that it was reclassifying Subject 005974 as Progressive Disease, based on the proposed changes to the tumor assessment criteria. For Subject 004240 in Protocol BT-22, the Tumor Measurements CRF shows that the subject had a baseline MRI taken on February 21, 1996. The subject began receiving investigational drug on March 6, 1996, and had additional MRIs taken on April 10, May 22, June 26, and July 31, 1996. The Tumor Measurements CRF documents that a change of less than 50% change in tumor size, compared to baseline, was maintained only from April 10 through May 22, 1996, which is less than 12 weeks. Therefore, the subject did not meet the criteria for Stable Disease. In BRI's April 5, 2013 written response, BRI stated that it was retaining the original assessment for this subject, based on the sponsor's proposed changes to the tumor assessment criteria. However, BRI's response for this subject

did not address the incorrect classification of Stable Disease that resulted from lack of a 12-week maintenance period.

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

6. 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.

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