**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 4040 North Central Expressway, Suite 300<br>Dallas, TX 75204<br>(214) 253-5200 Fax:(214) 253-5314<br>Industry Information: www.fda.gov/oc/industry | 01/07/2013 - 03/15/2013*<br>FEI NUMBER<br>3003426453 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

**TO:** Stanislaw R. Burzynski, M.D., Ph.D., Clinical Investigator

| FIRM NAME | STREET ADDRESS |
|---|---|
| Stanislaw R Burzynski, MD | 9432 Katy Rd |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Houston, TX 77055-6349 | Clinical Investigator |

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

**DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:**

## OBSERVATION 1

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

a. You failed to comply with protocol requirements related to the primary outcome, therapeutic response, for Studies BT-09, BT-10, BT-21, and BT-22 for 18 of 27 (67%) of study subjects reviewed during the inspection. Specifically:

Protocol BT-09:

Study BT-09, Section 10.0, Criteria for Therapeutic Response, Subpart 10.1, defines a complete patient for evaluation of antitumor activity as "***one who meets the entrance criteria, has complete*** (b)(4) ***reatment with antineoplastons A10 and AS2-1, and has been compliant with the procedures required in the protocol.***" Subpart 10.2, Complete Response (CR), defines Complete Response as ***"Complete disappearance of all contrast-enhancing tumor on neuroimaging studies, and ancillary radiographic studies if appropriate for 4 weeks or longer. Patient is off corticosteroids."*** Subpart 10.3, Partial Response (PR), defines Partial Response as ***"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 4 weeks or longer. No simultaneous increase in size of any lesion or the appearance of new lesions may occur. The corticosteroid dose is stable or decreasing."***

i. The following 2 of 4 study subjects who were assigned a therapeutic response of "CR" did not meet one or more of the protocol criteria noted above:

- Subject 005297
- Subject 007197

ii. The following 2 of 5 study subjects who were assigned a therapeutic response of "PR" did not meet one or more of the protocol criteria noted above:

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | DATE ISSUED |
|---|---|---|
| | Joel Martinez, Investigator<br>Cynthia F. Kleppinger, Investigator<br>Hugh M. Mcclure, Investigator | 03/15/2013 |

- Subject 004721
- Subject 008765

Protocol BT-10

Study BT-10, Section 7.2, Definitions, Subpart 7.2.1 defines a complete patient for evaluation as "***one who meets the entrance criteria, has complete*** (b)(4) ***eatment with antineoplastons A10 and AS2-1, and has been compliant with the procedures required in the protocol.***" Subpart 7.2.3 defines Complete Response as "***Complete disappearance of all contrast enhancing tumor on neuroimaging studies, and ancillary radiographic studies if appropriate for a minimum duration of four weeks. Patient is off corticosteroids.***" Subpart 7.2.4 defines Partial Response as "***More than 50% reduction in the sum of the products of the greatest perpendicular diameters of all measurable contrast enhancing lesions, compared to the corresponding baseline evaluation for four weeks or longer. No simultaneous increase in size of any lesion or the appearance of new lesions may occur. The corticosteroid dose is stable or decreasing.***" Subpart 7.2.5 defines Stable Disease as "***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. This state must be maintained for a minimum of 12 weeks to qualify for stable disease. The corticosteroid dose is stable or decreasing.***"

iii. The following 3 of 3 study subjects who were assigned a therapeutic response of "CR" did not meet one or more of the protocol criteria noted above:

- Subject 06389
- Subject 11819
- Subject 13660

iv. The following 2 of 2 study subjects who were assigned a therapeutic response of "PR" did not meet one or more of the protocol criteria noted above:

- Subject 21428
- Subject 23399

v. The following 5 of 7 study subjects reviewed who were assigned a therapeutic response of "SD" did not meet one or more of the protocol criteria noted above:

- Subject 005974
- Subject 011373

- Subject 012184
- Subject 012206
- Subject 12252

Protocol BT-21:

Study BT-21, Section 10.0, Criteria for Therapeutic Response, Subpart 10.2, Complete Response (CR), defines Complete Response as ***"Complete disappearance of all contrast-enhancing tumor on neuroimaging studies, and ancillary radiographic studies if appropriate for 4 weeks or longer. Patient is off corticosteroids."*** Subpart 10.3, Partial Response (PR), defines Partial Response as ***"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 4 weeks or longer. No simultaneous increase in size of any lesion or the appearance of new lesions may occur. The corticosteroid dose is stable or decreasing."***

vi. The following 1 of 2 subjects who were assigned a therapeutic response of "CR" did not meet one or more of the protocol criteria noted above:

- Subject 009990

vii. The following 1 of 2 subjects who were assigned a therapeutic response of "PR" did not meet one or more of the protocol criteria noted above:

- Subject 004881

Protocol BT-22:

Study BT-22, Section 7.2, Subpart 7.2.1, defines a complete patient for evaluation of antitumor activity as "***one who meets the entrance criteria, has complete*** (b)(4) ***eatment with Antineoplastons A10 and AS2-1, and has been compliant with the procedures required in Protocol.***" Subpart 7.2.3 defines Complete Response as ***"Complete disappearance of all contrast enhancing tumor on neuroimaging studies, and ancillary radiographic studies if appropriate for a minimum duration of four weeks. Patient is off corticosteroids."*** Subpart 7.2.4 defines Partial Response as ***"More than 50% reduction in the sum of the products of the greatest perpendicular diameters of all measurable contrast enhancing lesions, compared to the corresponding baseline evaluation for four weeks or longer. No simultaneous increase in size of any lesion or the appearance of new lesions may occur. The corticosteroid dose is stable or decreasing."*** Subpart 7.2.5 defines Stable Disease as ***"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. This state must be maintained for a minimum of 12 weeks to qualify for stable disease. The corticosteroid dose is stable or decreasing."***

viii. The following study subject (1 of 1) who was assigned a therapeutic response of "PR"; did not meet one or more of the protocol criteria noted above:

- Subject 006239

ix. The following study subject (1 of 1) who was assigned a therapeutic response of "SD" did not meet one or more of the protocol criteria noted above:

- Subject 004240

b. You failed to assure that all subjects met the inclusion and did not meet exclusion criteria of the study protocols as evidenced by the following examples:

i. BT-09 Subject 23643: The study protocol required the subject to be off chemotherapy for at least 4 weeks. The subject discontinued chemotherapy on 7-17-12 and began treatment with the investigational product, antineoplastons (ANP) one day later, on 7-18-12.

ii. BT-22 Subject 8198: The protocol required that subjects have a Karnofsky Performance Scale (KPS) of 60% to 100% at baseline to be eligible for the study. KPS was not evaluated at baseline for this subject.

iii. BT-10 Subject 13677: The protocol required evidence of brain tumor by MRI or CT scan. For Subject 13677, the case history notes that the subject has atypical myxopapillary ependymoma throughout the spine with negative MRI of brain.

c. Protocol BT-22, Section 7.4.2.1, required arrangements to be made, prior to entering the patient in the study, for a physician in the patient's local area to provide continuing medical care and collect and report the data required in the protocol. Subject 011234 was consented on 1/10/07 and received first dose of study medication 1/11/07. You received a letter dated 1/19/07 from the subject's private physician in (b) (6) agreeing to provide supportive medical care but refusing to be involved with the protocol or participate in any protocol procedures. You did not make other arrangements for involvement of a physician in the patient's local area prior to entering the patient in the study.

d. You failed to comply with Study BT-22 requirements for discontinuation of study treatment.

- Appendix G of the study protocol requires antineoplaston (ANP) treatment be discontinued in patients until a serum sodium level of less than or equal to 147 mmol/L has been achieved.

i. Subject 21305 had a serum sodium of 148 mmol/L reported on 10/5/11. The ANP treatment was not discontinued until 10/10/11. Subject resumed treatment on 10/13/11. Subject had a serum sodium of 159 mmol/L reported on 10/13/11. The ANP was not discontinued until (b) (6) when the subject was admitted to the hospital for left-sided facial palsy, increased intracranial pressure and hypernatremia.

- Section 7.1.5.2 of the protocol states "***Patients should be removed from treatment for a third episode of Grade 3 or 4 toxicity or for any Grade 4 toxic effect that is truly life threatening or is not easily and rapidly reversible.***"

ii. Subject 4570 had the following serum sodium levels with protocol specific grading:
- Sodium level on 7/19/96 was 157 mEq/L Grade 3
- Sodium level on 7/23/96 was 155 mEq/L Grade 3
- Sodium level on 7/25/96 was 158 mEq/L Grade 3
- Sodium level on 7/26/96 was 166 mEq/L Grade 4
- Sodium level on 7/29/96 was 160 mEq/L Grade 4
- Sodium level on 8/06/96 was 160 mEq/L Grade 4

Subject was not terminated from the study treatment until 9/26/96.

iii. Subject 9896 had the following serum sodium levels with protocol specific grading:
- Sodium level on 11/19/04 was 164 mEq/L Grade 4
- Sodium level on 11/29/04 was 157 mEq/L Grade 3
- Sodium level on 11/30/04 was 157 mEq/L Grade 3
- Sodium level on 12/01/04 was 157 mEq/L Grade 3
- Sodium level on 12/22/04 was 156 mEq/L Grade 3
- Sodium level on 12/23/04 was 155 mEq/L Grade 3
- Sodium level on 12/26/04 was 162 mEq/L Grade 4

Subject was not terminated from the study treatment until 1/29/05.

e. Not all Adverse Events (AE) experienced by study subjects during their participation in the studies were reported to the sponsor as required by the study protocols. For example:

| Study Number | Subject Number | Date of AE | AE Description |
|---|---|---|---|
| AD-02 | 010526-05 | 11/04/2005<br>11/07/2005<br>11/14/2005<br>11/16/2005<br>11/22/2005<br>11/25/2005 | Hypernatremia (165 meq/L)<br>Hypernatremia (152 meq/L)<br>Hypernatremia (159 meq/L)<br>Hypernatremia (156 meq/L)<br>Hypernatremia (156 meq/L)<br>Hypernatremia (202 meq/L) |
| BT-09 | 004721 | 01/15/1997 | Twitching uncontrollably, cold sweats, hair loss, frequent urination, incontinence, headaches, confusion, numbness and weakness-arms/legs |
| BT-09 | 004721 | 02/19/1997 | Headaches, tunnel vision |
| BT-09 | 007197 | 06/21/2001<br>07/18/2001<br>10/29/2001 | Hypernatremia (152 meq/L)<br>Hypernatremia (151 meq/L)<br>Hypernatremia (153 meq/L) |

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| | | | |
|---|---|---|---|
| | | 01/07/2002 | Hypernatremia (151 meq/L) |
| BT-09 | 007554 | 10/30/2001<br>12/02/2001<br>07/10/2002<br>01/21/2002<br>01/28/2002<br>02/04/2002<br>02/08/2002<br>05/23/2002<br>08/19/2002 | Hyponatremia (125 meq/L)<br>Hyponatremia (123 meq/L)<br>Hyponatremia (129 meq/L)<br>Hypernatremia (155 meq/L)<br>Hypernatremia (153 meq/L)<br>Hypernatremia (152 meq/L)<br>Hypernatremia (156 meq/L)<br>Hypernatremia (151 meq/L)<br>Hypernatremia (152 meq/L) |
| BT-09 | 020416 | 04/23/2011<br>02/16/2012 | Hypokalemia (2.6 meq/L)<br>Hypokalemia (2.9 meq/L) |
| BT-09 | 022914 (SPP) | 10/29/2012 | Hyponatremia (129.0 meq/L) |
| BT-10 | 023612 | 07/21/2012<br>08/06/2012<br>08/10/2012<br>08/28/2012<br>09/14/2012<br>09/22/2012<br>11/27/2012 | Rash-surgical site<br>Fever (103° F)<br>Weakness, Fatigue<br>Nausea, fatigue, dizziness<br>Arthralgias<br>Nausea, Vomiting<br>Sprain, right ankle |
| BT-21 | 007341 (SPP) | 06/10/2001<br>08/13/2001 | Hypernatremia (153.0 meq/L)<br>Hypernatremia (149.0 meq/L) |

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

Forty-eight (48) subjects experienced 102 investigational drug overdoses between January 1, 2005 and February 22, 2013, according to the Weekly List of Hospitalizations/SAE/ANP Overdose (AO)/Catheter Infection report. Overdose incidents have been reported to you on a weekly basis during your Monday, Wednesday, and Friday staff meetings. There is no documentation to show you have implemented corrective actions during this time period to ensure the safety and welfare of subjects. The following are examples of overdoses:

i. BT-09 Subject 023916 Overdose: On 11/1/12, the subject's husband accidentally misprogrammed the pump and infused 200 mL of the Astugenal (AS2-1) instead of the intended dose of 25 mL x 6 times a day for a total dose of 150 mL in a 24 hour period. Subject became somnolent and had worsening of slurred speech and headache.

ii. For BT-10 Subject 019813, there were several incidences of overdose.
- Overdose 2/19/12: The pump was misprogrammed by the subject's father which resulted in the subject receiving 210 mL of Astugenal (AS2-1) within 2.5 hours instead of 24 hours. The subject then experienced pronounced somnolence.
- Overdose 5/5/11: The pump was misprogrammed by the subject's father. The subject received 245 mL of Astugenal (AS2-1) over approximately 2 hours instead of 24 hours resulting in somnolence.
- Overdose 4/30/11: The pump was misprogrammed by the subject's mother. The subject received 250 mL of Atengenal (A-10) at once and 250 mL (AS2-1) instead of 35 mL resulting in somnolence and a headache.
- Overdose 4/5/11: The IV tubing was switched accidentally by the subject's mother. The subject received 250

mL of Astugenal (AS2-1) instead of the intended dose of 35 mL resulting in somnolence, nausea, and vomiting.

iii. For BT-21 Subject 021257 Overdose: On 8/19/11, the subject's wife misprogrammed the pump infusing 250 mL of Astugenal (AS2-1) within 10 minutes instead of the intended dose of 40 mL every 4 hours over a 24 hour scheduled dose, resulting in a persistent focal seizure.

iv. For BT-22 Subject 021912 Overdoses: On 11/30/11 the subject's father accidentally switched the IV tubing, infusing 160 mL instead of 15 mL of the Astugenal (AS2-1) within 2 hours. Subject experienced somnolence. On 3/15/12 subject's mother accidentally switched the line, infusing 165 mL instead of 15 mL of Astugenal (S2-1) within an hour, with the subject experiencing somnolence.

v. For BT-10 Subject 13677 Overdose: On 3/19/12 the subject's mother accidentally misprogrammed the pump, infusing 242 mL of Astugenal (AS2-1) over 6 hours instead of the intended dose of 30 mL. The subject developed bilateral tinnitus.

There were also several overdoses recorded in the subjects' charts that were not captured in the Weekly List of Hospitalizations/SAE/ANP Overdose (AO)/Catheter Infection report as they occurred prior to the beginning of the captured reporting period (January 1, 2005). For example,

vi. For BT-22 Subject 7453 Overdose: On 9/20/01, the subject accidently received 180 mL of Astugenal (AS 2-1) at once instead of the intended dose of 30 mL. Subject became increasingly less responsive and was admitted to the hospital ICU (b) (6) and intubated. Subject was discharged from the hospital (b) (6)

vii. For BT-22 Subject 8198 Overdose: On 6/10/02, the subject accidently received 250 mL of Astugenal (AS2-1) at once instead of the intended dose of 30 mL. Subject became fatigued and slept several hours.

## OBSERVATION 2

Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Specifically,

a. Your MRI tumor measurements initially recorded on worksheets at baseline and on-treatment MRI studies for all study subjects were destroyed and are not available for FDA inspectional review.

b. Original case report forms (CRFs) for studies BT-09, BT-10, BT-21, and BT-22 on which data were originally recorded

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and reported to the Sponsor were not available for FDA inspection and review. As stated by study personnel, original CRFs were not retained with the revised CRF versions. Per the Study Subject Manual MQA-002 Revision A, dated 24 May 04, Section 4:

***"It is the investigator's responsibility to ensure that all forms completed by the clinical trial personnel are current. All information recorded on obsolete forms will be redone on the correct form. Information collected on obsolete documents will be marked with a single line through the document, with the initials/date of the investigator (or representative). This document will be stapled to the correct and completed form. All personnel handling the documents are responsible for ensuring all source and case report forms are filed immediately to avoid lost or misplaced subject information."***

c. You did not adequately and accurately capture all Adverse Events (AEs) experienced by study subjects during their participation in Study BT-09. Specifically:

| Study Number | Subject Number | Date of AE | AE Description |
|---|---|---|---|
| BT-09 | 011905 | 05/30/2008 | Hypernatremia (169 meq/L), AE CRF reports Grade 3. However, according to the grading scale that was used (CTCAE 3.0) the AE should have been graded 4. |
| BT-09 | 005361 | 03/2/1998 | Hypernatremia (161 meq/L), AE CRF reports Grade 2. However, according to the grading scale that was used (CTCAE 3.0) the AE should have been graded 4. |

## OBSERVATION 3

Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

Specifically, per the Study Subject Manual MQA-002 Revision A, dated 24 May 04 Section 10.2.14 "***Investigator and RA report to the IRB/EC all SAE [sic] within 10 working days***".

Concerning BT-22 Subject 5960

- Subject was admitted to the hospital (b) (6) for pneumonia. This SAE was not reported to the IRB until 3/29/05.
- Subject was admitted to the hospital for bronchitis and UTI (b) (6). This SAE was not reported to the IRB until 3/29/05.
- Subject was admitted to the hospital for increased intracranial pressure, fever and cough with loss of consciousness (b) (6) This SAE was not reported to the IRB until 3/29/05.
- Subject was admitted to the hospital on (b) (6) for confusion, metabolic acidosis and cranial bleed. This SAE was not reported to the IRB until 3/29/05.

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|---|---|---|
| | Joel Martinez, Investigator JM.<br>Cynthia F. Kleppinger, Investigator<br>Hugh M. Mcclure, Investigator | 03/15/2013 |

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## OBSERVATION 4

The informed consent document did not include a statement of any additional costs to the subject that might result from participation in the research, as appropriate.

Specifically,
The informed consent document did not include a statement of any additional costs to the subject that might result from participation in the research, as appropriate.

Specifically,

In the Study Monitoring Plan, MQA-001 Revision A, Section 13.1.7 it states "the informed consent form and explanation includes:

- Any additional costs to the subject that may result from participation in the research"

The informed consent document (ICD) did not include or reference a separate treatment billing agreement as part of the informed consent process. For 5 of 16 subjects for whom the treatment billing agreement was reviewed, the informed consent document was signed days to weeks prior to the treatment billing agreement:

- BT-22 Subject 021925: This subject signed the ICD on 11/07/11 and the treatment billing agreement on 11/10/11.
- BT-21 Subject 021112: This subject signed the ICD on 8/02/11 and the treatment billing agreement on 8/08/11.
- BT-21 Subject 022124: This subject signed the ICD on 11/14/11 and the treatment billing agreement on 12/6/11.
- BT 10 Subject 011819: This subject signed the ICD on 3/26/08 and the treatment billing agreement on 3/28/08.
- BT 10 Subject 021341: This subject signed the ICD on 8/18/11 and the treatment billing agreement on 8/26/11.

## OBSERVATION 5

Legally effective informed consent was not obtained from a subject or the subject's legally authorized representative, and the situation did not meet the criteria in 21 CFR 50.23 - 50.24 for exception.

Specifically, a signed informed consent document was not found for the following subjects:

- BT-22 Subject 5586
- (b) (4) Subject 9896

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## OBSERVATION 6

Investigational drug disposition records are not adequate with respect to quantity and use by subjects.

Specifically,

a. Discrepancies exist between the amount of A10 Antineoplastons bags received from the (b) (4) manufacturing facility and the amount dispensed to subjects. For example:

| Batch (b) (4) | Quantity Received | Quantity Dispensed | Bags Unaccounted for |
|---|---|---|---|
| | 248 | 230 | 18 |
| | 253 | 246 | 7 |
| | 245 | 246 (dispensed one additonal than what actually received) | |

b. Four subjects' records (009270, 22124, 21341, and 21925) from Studies (b) (4) BT-21, BT-10 and BT-22 were selected at random to determine a full drug accountability of the A10 antineoplaston. The review determined there are approximately 159 bags unaccounted for Subject 009270, approximately 29 bags for Subject 22124, approximately 23 bags for Subject 21341 and approximately 17 bags for Subject 21925.

*** DATES OF INSPECTION:**
01/07/2013(Mon), 01/08/2013(Tue), 01/09/2013(Wed), 01/10/2013(Thu), 01/11/2013(Fri), 01/14/2013(Mon), 01/15/2013(Tue), 01/16/2013(Wed), 01/17/2013(Thu), 01/18/2013(Fri), 01/22/2013(Tue), 01/23/2013(Wed), 01/24/2013(Thu), 01/25/2013(Fri), 01/28/2013(Mon), 01/29/2013(Tue), 01/30/2013(Wed), 01/31/2013(Thu), 02/01/2013(Fri), 02/19/2013(Tue), 02/20/2013(Wed), 02/21/2013(Thu), 02/22/2013(Fri), 02/26/2013(Tue), 02/27/2013(Wed), 02/28/2013(Thu), 03/01/2013(Fri), 03/12/2013(Tue), 03/15/2013(Fri)

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