U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Summers, Timothy, MD 2/24/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 209938

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 10-HFD-45-01-02

Timothy Summers, M.D.
Alliance Health Center
5000 Highway 39 N
Meridian, MS 39301-1021

Dear Dr. Summers:

Between March 25 and 27, 2009, Ms. Barbara Wright, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation [Protocol **(b)(4)**, entitled "**(b)(4)**"] of the investigational drug **(b)(4)** performed for **(b)(4)** Inc.

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, 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 are aware that at the conclusion of the inspection, Ms. Wright presented and discussed with you Form FDA 483, Inspectional Observations. You have not provided a written response to the Form 483. By letter of April 27, 2009, Alliance Health Center (AHC) responded to the Form 483, recognizing that the facility and you failed to adequately address certain protocols. ACH also indicated that you were no longer conducting clinical research at the AHC facility. We wish to emphasize the following:

1. You failed to conduct the studies or ensure they were conducted according to the signed investigator statement and the investigational plan, and to protect the rights, safety, and welfare of subjects under the investigator's care [21 CFR 312.60].

a. Eligibility criteria are designed specifically for each clinical investigation by the sponsor to optimize the interpretability of the data to the disease process under study and to minimize foreseeable harm of enrolled subjects due to co-morbidities and possible interactions with concomitant medications. Three of the six subjects randomized in this clinical investigation did not meet eligibility criteria of having Bipolar I Disorder and as such were placed at risk of injury from participation in the study. Specifically:

i. The protocol eligibility criteria state that a "subject must have a primary diagnosis of Bipolar I Disorder … as defined by the DSM-IV criteria and confirmed by the [Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS)]." Subject 1001 was screened and randomized to the study without a primary diagnosis of Bipolar I disorder confirmed by a fully-completed K-SADS assessment. In particular, the K-SADS assessment for Subject 1001 did not contain the indicated Depressive

Disorders and the Mania supplements.

ii. The protocol eligibility criteria state that a subject must have a Young Mania Rating Scale (YMRS) score greater than or equal to 17 at the screening and baseline visits. Subjects 1009 and 1010 were each randomized to the study with a YMRS score of 8 at baseline.

b. The protocol states that the first dose of the study medication is taken at the baseline visit after completion of baseline visit procedures to confirm subject eligibility and to perform post-dosing pharmacokinetic (PK) sampling. Subject 1010 was dosed on December 8, 2006, three days prior to the baseline visit on December 11, 2006 and as such did not have eligibility confirmed and did not have PK sampling performed.

c. The protocol requires that efficacy be assessed using the YMRS, the Children's Global Assessment Scale (CGAS), and Clinical Global Impression (CGI) scale at each visit. The CGI assessment was not performed at the Week 1 study visit for Subject 1010.

d. You failed to follow protocols related to the enrollment of wards of the state. The Institutional Review Board (IRB) "Initial Review Submission Form" Box 28 in this study addressed "vulnerable" subject categories. You failed to indicate that you intended to enroll Subjects 1001 and 1007, both wards of the state and thus vulnerable subjects, to the IRB on the Initial Review Submission Form. In turn, the IRB was prevented from assessing whether it was appropriate to enroll wards of the State in this particular clinical investigation and was prevented from requiring that an advocate be appointed for each child who is a ward pursuant to 21 CFR 50.56.

Enrollment of subjects who do not meet eligibility criteria, and not performing study-related procedures jeopardize subject safety and welfare and compromise interpretation and validity of the investigational endpoints.

2. You failed to maintain adequate and 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 [21 CFR 312.62(b)].

During the inspection, the study records (including study templates and assessment tools) were observed to be unbound and appeared to lack a system of controls, with entries posted to the wrong visit form and multiple versions completed for the same visit. Subject records contained missing pages, numerous unexplained corrections and conflicting information. Few progress notes were observed Violations included, but were not limited to, the following:

a. The protocol eligibility criteria state that a subject must have a YMRS score greater than or equal to 17 at the screening and baseline visits. Study records for Subject 1006 contained two sets of original records with different scoring for the YMRS assessments reportedly obtained during the October 31, 2006 study visit. One of the copies of the YMRS for Subject 1006 dated October 31, 2006 has a score of 11 and the other copy has a score of 23. You provided no explanation for the discrepancies in these records.

b. The K-SADS-Present and Lifetime Version is a multi-part diagnostic interview instrument that consists of a screening interview and five additional diagnostic supplements. The additional diagnostic supplements may be indicated based upon scores obtained as determined by the answers given by the subject during the screening interview. The KSADS-PL for Subjects 1001, 1004 and 1006 were missing every other page and/or the required supplements.

c. The records for Subject 1004 contained numerous errors in subject number, protocol number, and date or identity of study visit. For example:

i. Numerous records reflect that subject number 1002 was used instead of the correct subject number 1004.

ii. Forms marked "Screening Visit," "Week 1 Visit," and "Week 4 Visit" all are dated October 31, 2006.

iii. There are two forms marked "Week 1 Visit" documenting the Children's Depression Rating Scale Revised (CDRS-R) evaluation with two different dates, October 31, 2006 and November 8, 2006.

iv. You utilized a form from another study entitled " Study" to document testing completed on this subject for this study.

Failing to maintain adequate and accurate case histories compromises the interpretation of and the validity of the clinical investigational **endpoints.**

3. You failed to obtain informed consent of each subject in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].

Except as provided in 21 CFR 50.23 and 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally-effective informed consent of the subject or the

subject's legally authorized representative [21 CFR 50.20].

As an investigator, it is your responsibility to obtain informed consent in accordance with 21 CFR Part 50. Except as provided in 21 CFR 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form [21 CFR 50.27(a)].

You failed to obtain legally-effective informed consent from Subject 1001 to whom you prescribed the investigational new drug, **(b)(4)**. Specifically, the informed consent form for Subject 1001 in Protocol **(b)(4)** was signed only by a parent and not by a representative of the Mississippi State Department of Human Services. At the time of the clinical investigation, the child was in the legal custody of the Mississippi State Department of Human Services and thus only the Mississippi State Department of Human Services could serve as the child's legally-authorized representative and grant permission for the child to participate in the clinical investigation.

Failing to obtain adequate informed consent jeopardizes the safety and welfare of enrolled subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

4. You failed to promptly report to the IRB all changes in the research activity and you made changes in the research without IRB approval [21 CFR 312.66].

FDA regulations require that the clinical investigator shall assure that he will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research with IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects [21 CFR 312.66].

You violated this requirement by administering the investigational new drug **(b)(4)**, to Subject 1010 without obtaining IRB approval of the modified informed consent document. Specifically, the IRB-approved version of the informed consent document for Protocol **(b)(4)** was altered by hand to state that the subject would not receive payment for participation in accordance with the schedule listed on the form unless treated as an outpatient, and this altered form was signed by the parent of Subject 1010.

Failure to promptly report changes in the research activity to the IRB and making changes in the research without IRB approval compromises the safety and welfare of subjects enrolled in the clinical 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 on-going 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 adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, 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 Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

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

/s/

LESLIE K BALL
02/04/2010

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