DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

David Linden, M.D.
Linden Research Consultants
1608 NW Expressway
Oklahoma City, OK 73118

Dear Dr. Linden:

By letter dated 5/22/07, the Food and Drug Administration (FDA), Center for Drug Evaluation and Research, issued a Warning Letter sent by certified mail to you at your former address of 6406 N. Santa Fe, Oklahoma City, OK.

The certified mail was returned to us. For this reason, we are re-issuing the Warning Letter to you at your current address. Except for the change of address, this Warning Letter is identical to the one dated 5/22/07.

Enclosed you will find a copy of the Warning Letter.

Sincerely yours,

{See appended electronic signature page}

Gary Della'Zanna, D.O., M.Sc.
Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

David Linden, M.D.
Linden Research Consultants
1608 NW Expressway
Oklahoma City, OK 73118

Ref: 07-HFD-45-0301

Dear Dr. Linden:

Between April 12 and May 25, 2006, Ms. Margaret Annes, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of clinical investigations. The following protocols were audited; protocol [ ] entitled "A randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and tolerability of [ ] in the treatment of manic episodes of bipolar I disorder over 3 weeks" of the investigational drug [ ] performed for [ ] and protocol [ ] entitled [ ] Versus Aripiprazole in the treatment of Acutely Ill Patients with schizophrenia" of the investigational drug [ ] performed for [ ]

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, the documents submitted with that report and your June 21, 2006, letter written in response to the Form FDA 483, Inspectional Observations, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Annes presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to protect the rights, safety, and welfare of subjects under your care [21 CFR 312.60].**

   Specifically, you refused to allow subject 022 to discontinue her participation in protocol [ ] and leave your controlled access inpatient research facility. The subject signed the consent form to participate in the study on May 29, 2005. The

consent form specified that "your participation in this research is voluntary. You may refuse to enroll, or change your mind at any time. If you say "yes" now, you can say "no" and stop later. There will be no penalty to you. ... If you want to stop being in the study, tell the study doctor or study staff." A patient status report for the subject, dated June 3, 2005, states that "after talking with her lawyer, she said the doctor would not let her leave because her husband lied on her." An Oklahoma City Police Department report, dated June 3, 2005, documented a call to police and police response "in reference to a disturbance over a patient wanting to leave." The subject's attorney sent you a letter, dated June 6, 2005, documenting a conversation with you on June 3, 2005, regarding the subject's desires to be released from the facility. Progress notes, dated June 4, 2005 and June 5, 2005, document that the subject continued to participate in the study. The subject was randomized in the study on June 5, 2005, and received the first dose of study medication on June 6, 2005. The subject's lawyer confirmed in an interview that the subject, in his presence, asked the staff to let her leave, but that her requests to leave were denied and that she was only allowed to discontinue her participation in the study after the lawyer signed her out of your facility on June 7, 2005. We find your June 21, 2006, response to this violation inadequate.

2. **You failed to obtain informed consent of subjects involved in research [21 CFR 50.20 and 21 CFR 312.60].**

Regarding protocol [redacted]

a. Subject 016 [redacted] was randomized in this double blind, placebo controlled study and received study drug from April 11, 2005-April 19, 2005. However, the subject did not sign a consent form to participate in this study. Instead, the subject signed a consent form to participate in an open label study, protocol [redacted]

b. A blood sample was drawn on March 16, 2005 from subject 012 [redacted] for pharmacogenetic analysis. However, this subject did not sign the protocol required consent form to participate in the pharmacogenetic component of the study.

Regarding Protocol [redacted]

c. Subjects 2003 [redacted] 2004 [redacted] 2005 [redacted] 2006 [redacted] 2007 [redacted] and 2008 [redacted] did not sign the current IRB-approved version of the consent form which contains additional information pertaining to risk. Specifically, on 2/5/05, subject 2003 signed the consent form approved by the IRB on 7/1/04, but should have signed the updated version of the consent form approved by the IRB on 11/3/04. On 3/28/05, subject 2004 signed the consent form approved by the IRB on 7/1/04, but should have signed the updated version of the consent form approved by the IRB on 11/3/04. On 5/9/05, subject 2005 signed the consent form approved by the IRB on 11/3/04, but should have signed the updated version of the consent form approved by the IRB on 4/6/05. On 5/19/05, subject 2006 signed the consent form approved by the IRB on 11/3/04, but should have signed the updated version of the consent form approved by the IRB on 4/6/05. On

5/30/05, subjects 2007 and 2008 signed the consent form approved by the IRB on 7/1/04, but should have signed the updated version of the consent form approved by the IRB on 4/6/05.

In your June 21, 2006, response to the Form FDA 483, Inspectional Observations, you acknowledged and accepted responsibility for this violation. We acknowledge your assurances that corrective actions will be taken to prevent similar findings from occurring in any future studies.

3. **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].**

   a. Protocol[ ] specified that all subjects must be hospitalized for the baseline visit and the first 2 weeks of the treatment phase. The status of High Pointe changed from a licensed hospital to an unlicensed facility in February 2005. You did not notify the IRB of the change in status of the hospital and housed study subjects at the unlicensed facility without IRB approval.

In your June 21, 2006, response to the Form FDA 483, Inspectional Observations, you acknowledged and accepted responsibility for these violations. We acknowledge your assurances that corrective actions will be taken to prevent similar findings from occurring in any future studies.

4. **You failed to conduct the studies or ensure they were conducted according to the investigational plan (approved protocols) [21 CFR 312.60].**

   Regarding protocol[ ]

   a. The maximum daily dose of study drug was changed to 2000 mg/d in Amendment 1 of the protocol approved by the IRB 10/1/04. Subjects 001 and 002 received dosages greater than the maximum daily dose. Specifically, subject 001 received 2500 mg/d of study drug daily from 1/19-26/05 and subject 002 received 2500 mg/d of study drug daily from 1/26-27/05.

   b. The protocol specifies that the Young Mania Rating Scale (Y-MRS) must be conducted by a rater who is not directly or indirectly involved with the patient's treatment before or during the study (independent rater). Y-MRS for subjects 001 and 015 were conducted by raters who were involved with the subjects' care. Specifically;

      i) Subject #001: The screening and baseline Y-MRS were performed by[ ]on 12/29/04 and 1/5/05. [ ]was involved in the subject's care by performing the MINI on 12/29/04, and the Hamilton Psychiatric Rating Scale for Depression (HAMD), The Brief Psychiatric Rating Scale (BPRS) and the Clinical Anxiety Scale (CAS) on 1/5/05.

      ii) Subject #015: [ ]performed the Y-MRS for this subject at the baseline visit on 3/29/05, at Visit 3 on 4/2/05, at Visit 4 on 4/5/05 and at Visit 5 on 4/12/05. [ ]was involved in the subject's care by performing the Psychlinx Initial

Mental Health Assessment on 3/21/05. At Visit 6 on 4/19/05,[ ]performed the Y-MRS. As the Study Coordinator,[ ]was involved in the subject's care since the screening visit on 3/22/05, and performed the Hamilton Depression Rating Scale (HAMD) for this subject on 4/19/05.

c. The protocol states that "every SAE (serious adverse event) occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported to[ ]within 24 hours of learning of its occurrence."

   i) The discharge summary for subject 002 indicates that the subject was considered unstable and was placed under an Emergency Order of Detention (EOD) and transferred to a hospital for psychiatric care on 2/7/05, 6 days after the subject completed the study. This was not reported to the sponsor as an SAE. We find your response dated June 21, 2006, to this violation unacceptable.

   ii) Subject 008 was randomized into the study and received the first dose of study medication on 3/3/05. The subject was placed under an Emergency Order of Detention (EOD) and transferred to a hospital for psychiatric care on 3/14/05. This was not reported as an SAE to the sponsor until 6/21/05.

   iii) Subject 039 was randomized into the study and received her 1st dose of study medication on 9/22/05. The subject was placed under an Emergency Order of Detention (EOD) on 9/22/05 after she had to be taken to the crisis center for treatment. The SAE was not reported to the sponsor until 11/16/05.

Regarding Protocol[ ]

d. The protocol eligibility criteria specified that patients needing a thyroid hormone supplement to treat hypothyroidism must have been on a stable dose of the medication for at least 2 months prior to Visit 1". Subject #2016 had been taking Levoxyl for approximately 1 month and 11 days prior to visit 1.

e. The protocol specified that patients receiving more than one dose of[ ] (oral or IM) or aripiprazole within 72 hours prior to Visit 1 will be excluded from the study. Subject #2005 had been taking aripiprazole from 12/23/03-05/08/05. The subject signed the consent form for the study on 5/9/05 and was enrolled in the study.

In your June 21, 2006, response to the Form FDA 483, Inspectional Observations, you acknowledged and accepted responsibility for these violations.

5. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

Regarding protocol[ ]

a. The actual number of tablets returned for each randomization number was not

documented. The Drug Summary Log only contains the number of full, partial, and empty bottles that were returned.

b. The amount of study drugs dispensed to, and returned by, subjects 002, 005, 008, 015, and 020 cannot be determined. Specifically:

i) For subject 002, the Medication Record indicates that the subject received study medication from 1/12/05 to 2/1/05. The Drug Label Form contains 3 labels indicating that 13/250mg tablets, 25/500mg tablets and 52/500mg tablets were dispensed. The Drug Accountability Log indicates that 13/250mg tablets were dispensed (date unknown) and 4/250mg tablets returned on 1/14/05. It does not indicate that any other study drug was dispensed or returned.

ii) For subject 008, the Dosage Administration Record does not list a stop date for the study drug and there is no Medication Record.

iii) For subject 005, there is no Medication Record.

iv) For subject 015, the Medication Record indicates that the subject received 250 mg of the study drug on 3/30/05. The Dosage Administration Record indicates that the subject received 500 mg of the study drug on 3/30/05.

v) For subject 020, the Medication Record and the Dosage Administration Record both indicate that the subject received study drug from 5/5-24/05. There are two entries for each of the following dates: 5/21/05, 5/22/05 and 5/23/05. One entry shows that the subject received 2000mg of study drug on 5/21/05 and 1000mg of study drug on 5/22/05 and 5/23/05. The other entry on a separate sheet indicates that the subject received 1500mg on 5/21/05, 5/22/05 and 5/23/05. Therefore, it is not possible to tell which entry is correct, and how much study drug the subject received on 5/21/05, 5/22/05 and 5/23/05 and how much should have been returned.

6. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].

Regarding protocol [ ]

a. For subject 015, information in the Medication Record, Rescue Medication Tracking Log, and the Source Worksheet contain conflicting entries for the amount of rescue medication. The Medication Record indicates that the subject received rescue medication on 4/1/05 (1mg) and 4/4/05 (4mg), after the start of study drug. The Rescue Medication Tracking Log indicates that the subject only received rescue medication on 4/9/05 (1mg) after the start of the study drug. The source worksheet used to document concomitant medications/significant drug therapies after the start of the study drug indicates that the subject received rescue medication on 3/30/05 (4mg), 3/31/05 (4mg), 4/1/05 (2mg), 4/2/05 (4mg), 4/3/05 (2mg), 4/4/05 (4mg) and 4/9/05 (1mg).

b. For subject 022, the Rescue Medication Log indicates that the subject was only given rescue medication on 5/3/05. The Medication Record indicates that the subject received 3mg of rescue medication on 6/3/05, 6/4/05 & 6/5/05 and 1mg on 6/6/05.

In your June 21, 2006, response to the Form FDA 483, Inspectional Observations, you acknowledged and accepted responsibility for this violation.

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 or will be taking 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 (240) 276-8829, FAX (240) 276-8844. 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, HFD-46
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Gary Della'Zanna, D.O., M.Sc.
Director
Division of Scientific Investigations, HFD-45
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/

Gary DellaZanna
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