

Inspections, Compliance, Enforcement, and Criminal Investigations

Gazda, Thomas M.D. 11/24/09



Department of Health and Human Services

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

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 10-HFD-45-11-02

Thomas Gazda, M.D.
4383 N. 75th Street
Scottsdale, Arizona 85251

Dear Dr. Gazda:

Between January 20 and February 6, 2009, Ms. Tonia Sawyer, representing the Food and Drug Administration (FDA), conducted an investigation and met with Dr. **(b)(6)**, current Meadowbrook Research, Inc. clinical staff member; and Ms. Pamela Larson, President and CEO of Meadowbrook Research, Inc., to review your conduct of a clinical investigation **(b)(4)** of the investigational drug **(b)(4)** performed for **(b)(4)**.

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. We are aware that at the conclusion of the inspection, as you were no longer an employee of Meadowbrook Research, Inc., Ms. Tonia Sawyer presented and discussed with the sub-investigator, Dr. **(b)(6)**, Form FDA 483, Inspectional Observations. We note that on June 6, 2009, Ms. Tonia Sawyer delivered a copy of the Form FDA 483 to you at your current employer's address: 7575 E. Earll Drive, Scottsdale, Arizona 85251.

We acknowledge receipt of two letters, dated February 17, 2009, and February 26, 2009, from Meadowbrook Research, Inc's CEO, Ms. Pamela Larson, and the sub-investigator, Dr. **(b)(6)**, that were intended to respond to the Form FDA 483, Inspectional Observations. The response letters describe the actions that have been taken or that will be taken by Meadowbrook Research, Inc. to prevent similar violations in future studies conducted at Meadowbrook Research, Inc. However, as of November 20, 2009, FDA has not received a written response from you to the Form FDA 483, Inspectional Observations. As the principal clinical investigator, you are personally responsible for the conduct of the study, not Meadowbrook Research, Inc.

You should respond in writing explaining how you will ensure that such violations do not occur in any future clinical studies you conduct.

We wish to emphasize the following:

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

Specifically, there were numerous violations of the protocol that raise significant questions regarding the reliability of the data.

a. The protocol specified that the person obtaining informed consent must be sufficiently trained on medical issues, so that questions could be adequately addressed. The protocol specifically required that this person have an M.D., Ph.D., or RN degree; if the person did not have one of these degrees, then this person must have been approved by **(b)(4)** to obtain informed consent. For all subjects enrolled into this study (Subjects 1001-1008 and 1010-1013), the informed consent document and the assent form for children 10-17 years of age were not obtained by an M.D., Ph.D., or RN, as required by the protocol. In addition, you did not obtain **(b)(4)** approval for these persons to obtain informed consent and assent of the study subjects.

b. The protocol inclusion criteria specified that the subject must have a primary diagnosis of **(b)(4)** as defined by **(b)(4)** criteria and confirmed by the **(b)(4)** For Subjects 1008, 1010, 1011, 1012, and 1013, **(b)(4)** for **(b)(4)** diagnostic instrument was used in error

to confirm diagnosis at screening, instead of the **(b)(4)** instrument as required by the protocol.

c. The protocol required that the **(b)(4)** be administered by the principal investigator or a sub-investigator who was a **(b)(4)** or a Ph.D.-level **(b)(4)**, and who had participated in the **(b)(4)** rater-qualification program.

i. For Subjects 1001-1007, **(b)(4)** was not administered by the principal investigator or a sub-investigator, as required by the protocol. Instead, the **(b)(4)** was administered by a study coordinator, contrary to the criteria specified in the protocol.

ii. There was no documentation of **(b)(4)** training for the principal investigator or sub-investigators participating in the **(b)(4)** rater-qualification program, as required by the protocol.

d. The protocol required that after the baseline visit and through Study Week 2, the investigator or designated staff contact the subject and the subject's parent(s) and/or guardian(s) on a daily basis, either by telephone or in person, to ensure that the subject was taking the proper capsules at the proper time, and to monitor the tolerability and efficacy of the titration plan.

For 10 of the 11 enrolled subjects, there is no documentation that you or your designated staff contacted the subject and the subject's parent(s) and/or guardian(s) on a daily basis, either by telephone or in person, as required by the protocol.

e. The protocol specified that for subjects with a body weight < 45 kg, the target dose was 60-80 mg/day. On 10/5/06, Subject 1010's body weight was documented as 40.1 kg, and per protocol, the subject's initial study medication dose was 20 mg twice a day for a total of 40 mg/day. On 10/12/06, the subject's study medication dose was increased to 40 mg twice a day, which was the maximum allowable limit for this subject on study. However, on 10/15/06, this subject's study medication dose was increased again to 60 mg twice a day for a total of 120 mg per day, thus exceeding the maximum allowable study medication limit for this subject. This subject received 120 mg/day of study medication for five consecutive days while participating in this study.

f. The protocol required that one ECG be done at the screening visit and that three consecutive ECGs be done at the baseline visit. The baseline visit was to occur 1-10 days after the screening visit. Subject 1010 did not have an ECG performed at the screening visit on 9/29/06. Instead the screening ECG was completed on the same date that the three baseline ECGs were completed, at the baseline visit on 10/05/06.

g. The protocol required that all subjects have two pharmacokinetic samples drawn after taking the first dose of study medication (Day 1), 20 mg; the first sample was to be collected at 0.5-1.5 hours post first dose, and the second sample was to be collected 1.5-3 hours post first dose. These samples were not always collected within the protocol-required time periods. For example:

i. Subject 1010 took the first dose of study medication on 10/5/06 at 1730 hours; however, the source record for this subject showed that the first pharmacokinetic sample was collected at 1735 hours, only 5 minutes after taking the first dose. The pharmacokinetic post first dose draw time for this subject should have been between the hours of 1800-1900 on 10/5/06.

ii. Subject 1011 took the first dose of study medication on 10/31/06 at 1615 hours; however, the source record for this subject showed that the first pharmacokinetic sample was collected at 1630 hours, only 15 minutes after taking the first dose. The pharmacokinetic post first dose draw time for this subject should have been between the hours of 1645-1745 on 10/31/06.

h. The protocol specified that at the baseline visit, Day 1, subjects take their first dose of study medication, 20 mg. Following this first study medication dose, the subject was to have a pharmacokinetic sample drawn 0.5-1.5 hours post dose, and a second pharmacokinetic sample drawn at 1.5-3 hours post the first study medication dose. The protocol required that at the Week 4 visit, subjects take their morning dose of study medication. An ECG was to be administered, followed by a pharmacokinetic sample at 0.75-3.0 hours post study medication dose. Subjects were then to present at the clinic between 5-7 hours post study medication dose, when blood pressure and pulse (vitals) were to be measured, followed by another ECG. Ten minutes after the ECG administration, another pharmacokinetic sample was to be drawn. Finally, the protocol required that subjects who terminated from the study prior to Week 4 (Early Termination: ET) were to have pharmacokinetic samples taken and ECG and vital signs measured, as per the Week 4 visit procedures. These protocol-specified procedures were not always followed for 9 of 11 enrolled subjects. The table below lists, by subject, protocol-specified procedures that were not conducted at your site.

| Subject | Date | Protocol Visit | PK Sample Missed | ECG Missed | Vital Signs Missed |
|----------------|-------------|-----------------------|-------------------------|-------------------|---------------------------|
| 1002 | 7/08/06 | Week 4 | 5 hrs to 7 hrs | 5 hrs to 7 hrs | 5 hrs to 7 hrs |
| 1003 | 8/23/06 | Week 4 | 5 hrs to 7 hrs | N/A | 5 hrs to 7 hrs |
| 1004 | 8/16/06 | Day 1 | 1 hrs 30 min to 3 hrs | N/A | N/A |
| 1004 | 9/14/06 | ET | 5 hrs to 7 hrs | 5 hrs to 7 hrs | 5 hrs to 7 hrs |

| | | | | | |
|------|----------|--------|------------------------|----------------|----------------|
| 1005 | 8/31/06 | ET | 5 hrs to 7 hrs | 5 hrs to 7 hrs | 5 hrs to 7 hrs |
| 1007 | 9/28/06 | ET | 5 hrs to 7 hrs | | |
| 1008 | 10/11/06 | Week 4 | 5 hrs to 7 hrs | 5 hrs to 7 hrs | 5 hrs to 7 hrs |
| 1010 | 10/20/06 | ET | 5 hrs to 7 hrs | 5 hrs to 7 hrs | 5 hrs to 7 hrs |
| 1012 | 3/01/07 | Day 1 | 30 min to 1 hrs 30 min | N/A | N/A |
| 1012 | 3/01/07 | Day 1 | 1 hrs 30 min to 3 hrs | N/A | N/A |
| 1013 | 3/2/07 | Day 1 | 30 min to 1 hrs 30 min | N/A | N/A |
| 1013 | 3/2/07 | Day 1 | 1 hrs 30 min to 3 hrs | N/A | N/A |

ET Early Termination
Day 1 Baseline Date per Protocol
hrs Hours
min Minutes
N/A Not Applicable (not cited as a violation)

II. You failed to prepare and 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)].

Specifically, there were numerous inaccuracies in recordkeeping noted in records for 10 of 11 subjects enrolled into the study, which raises significant questions regarding the reliability of the data.

a. Examples of inaccurate case histories for Subject 1001 include, but were not limited to the following:

i. The screening visit source record, dated 6/2/06, documented the standing pulse as 98; however, the corresponding electronic CRF (eCRF) documented the standing pulse as 82. The screening visit source record entry for Family History of Disease documented **(b)(4)** under the "Biological Siblings" heading with "NA (4)" marked with an X; however, the corresponding eCRF had the same heading with "yes (1)" marked with an X.

ii. The Week 2 visit source record, dated 6/23/06, documented the standing pulse as 100; however, the corresponding eCRF documented the standing pulse as 88.

iii. The Adverse Event Log source record for an **(b)(4)** event recorded the stop date as 7/5/06; however, the eCRF documented the "Outcome of AE to Date" as "Date resolved 7/11/06."

b. Examples of inaccurate case histories for Subject 1002 include, but were not limited to the following:

i. The screening visit Primary Diagnosis source record entry, dated 6/2/06, documented the duration of current Primary Diagnosis episode (months) as zero (0) and number of prior Primary Diagnosis episodes as 0 (zero). However, the corresponding eCRF recorded the duration of current Primary Diagnosis episode (months) as 1 and the number of prior Primary Diagnosis episodes as 2.

ii. The Day 1 (Baseline) visit source record, dated 6/6/06, documented the standing blood pressure as 179/99; however, the corresponding eCRF, dated 6/9/06, documented the standing blood pressure as 119/99.

iii. The Week 4 visit source record, dated 7/05/06, documented the temperature as 37.1°C. However, the corresponding eCRF documented the temperature as 31.7°C.

c. Examples of inaccurate case histories for Subject 1003 include, but were not limited to the following:

i. The screening visit Primary Diagnosis source record, dated 7/21/06, documented the duration of current Primary Diagnosis episode (months) as zero (0) and number of prior Primary Diagnosis episodes as 0 (zero). However, the corresponding eCRF recorded the duration of current Primary Diagnosis episode (months) as 4 and the number of prior Primary Diagnosis episodes as 1.

ii. The Week 4 visit source record, dated 8/23/06, documented the supine blood pressure as 114/72 and pulse as 76, and the standing blood pressure as 111/70 and pulse as 90 (Predose). The corresponding eCRF recorded the supine blood pressure as 108/78 and pulse as 78, and the standing blood pressure as 100/64 and pulse as 80 (Pre-dose).

d. Examples of inaccurate case histories for Subject 1004 include, but were not limited to the following:

i. The screening visit source record, dated 8/1/06, titled **(b)(4)** History Questions," in Section 5: Family History of **(b)(4)**, Question 1 reads, **(b)(4)**?" The response box is marked "yes, uncle/aunt"; however, for the same question

on the eCRF, the box was marked "no."

ii. The Day 1 (Baseline) visit source record, dated 8/16/06, for the **(b)(4)**, Question 2, pertaining to **(b)(4)** was marked "(2)." The **(b)(4)** Question 3, pertaining to **(b)(4)**, was marked "(1) **(b)(4)**." The corresponding eCRF **(b)(4)** entry for Question 2, **(b)(4)** was marked "(1) **(b)(4)**," and Question 3, **(b)(4)**, was marked "(0) **(b)(4)**."

e. Examples of inaccurate case histories for Subject 1005 include, but were not limited to the following:

i. The screening visit Primary Diagnosis source record, dated 8/1/06, documented the duration of current Primary Diagnosis episode (months) as 0 (zero) and number of prior Primary Diagnosis episodes as 0 (zero). However, the corresponding eCRF recorded the duration of current Primary Diagnosis episode (months) as 2 (two).

ii. The Week 1 visit source record, dated 8/17/06, for **(b)(4)** Question 9, pertaining to **(b)(4)**, documented the response as **(b)(4)**. However, the corresponding eCRF **(b)(4)** Question 9 response was blank (i.e., nothing was marked).

f. Examples of inaccurate case histories for Subject 1007 include, but were not limited to the following:

The screening visit Primary Diagnosis source record, dated 8/31/06, documented the number of prior Primary Diagnosis episodes as 1 (one). However, the corresponding eCRF recorded the number of prior Primary Diagnosis episodes as 2 (two).

g. Examples of inaccurate case histories for Subject 1008 include, but were not limited to the following:

i. The screening visit Primary Diagnosis source record, dated 9/8/06, documented the duration of current Primary Diagnosis episode (months) as 0 (zero) and the number of prior Primary Diagnosis episodes as 3 (three). However, the corresponding eCRF recorded the duration of current Primary Diagnosis episode (months) as 1 (one) and the number of prior Primary Diagnosis episodes as 0 (zero).

ii. The screening visit Log Concomitant Drug Treatment source record, dated 9/8/06, had Prozac listed but then crossed out by R.M. on 11/9/06; however, the corresponding eCRF has Prozac listed on the "Previous Psychotropic Drug

Treatment" form.

h. Examples of inaccurate case histories for Subject 1010 include, but were not limited to the following:

i. The screening visit Primary Diagnosis source record, dated 9/29/06, documented the duration of current Primary Diagnosis episode (months) as 0 (zero). However, the corresponding eCRF recorded the duration of current Primary Diagnosis episode (months) as 2 (two).

ii. The screening visit source record, dated 9/29/06, documented waist circumference as "26.5" = 67.3 cm." However, the corresponding eCRF recorded the waist circumference (cm) as 26.5.

iii. The early termination visit source record, dated 10/20/06, documented height as 60.5". However, the corresponding eCRF recorded the height as 152.9 (cm) instead of the correct height in cm of 153.7.

i. Examples of inaccurate case histories for Subject 1011 include, but were not limited to the following:

The screening visit Primary Diagnosis source record, dated 10/20/06, documented the duration of the number of prior Primary Diagnosis episodes as 3 (three). However, the corresponding eCRF recorded the duration of the number of prior Primary Diagnosis episodes as 0 (zero).

j. Examples of inaccurate case histories for Subject 1012 include but were not limited to the following:

The screening visit Primary Diagnosis source record, dated 2/21/07, documented the duration of current Primary Diagnosis episode (months) as 0 (zero). However, the corresponding eCRF recorded the duration of current Primary Diagnosis episode (months) as 2 (two).

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 adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Tejashri Purohit-Sheth, M.D., at 301-796-3402; FAX 301-847-8750. Your written response and any pertinent documentation should be addressed to:

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5358
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
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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
11/24/2009