U.S. Food and Drug Administration
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Alexander Neumeister 2/19/16

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.: 16-HFD-45-02-01

Alexander Neumeister, M.D.
c/o Georges G. Lederman, Attorney at Law
52 Duane Street
7th Floor
New York, NY 10007

Dear Dr. Neumeister:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted from July 16 to August 5, 2015. Dr. Iram R. Hassan, representing FDA, reviewed your conduct of the following clinical investigations:

- Protocol **(b)(4)**, "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**.
- Protocol **(b)(4)**, "**(b)(4)**

This inspection is a part of 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, Dr. Iram R. Hassan presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of the August 19, 2015, written response to the Form FDA 483 submitted on your behalf by your attorney, Mr. Georges G. Lederman.

From our review of the FDA Establishment Inspection Report; the documents

submitted with that report; the July 22, 2015, letter from Mr. Lederman, memorializing the substance of Dr. Hassan's interview with you on July 16, 2015; and the written response dated August 29, 2015, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

1. 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)].

As a clinical investigator, you are required 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. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records, including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurse's notes. For Protocol **(b)(4)**, case histories include study records of required procedures such as medical history, psychiatric evaluations, physical and neurological examinations, and suicide risk assessments. You failed to maintain adequate and accurate case histories when your subinvestigator's name was recorded as having conducted certain required study procedures that, in fact, you or another study employee conducted. Examples of this failure include, but are not limited to, the following:

a. On worksheets for medical history, physical examinations, and neurological examinations, you personally hand-printed the name of your subinvestigator to indicate that these study procedures were conducted by your subinvestigator. However, in fact, you or another study employee actually conducted these study procedures, not your subinvestigator. Examples include the following:

i. Screening medical history for 2 subjects (Subjects 1 and 2)

ii. Screening physical examinations for all 14 enrolled subjects (Subjects 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 13, 14, 15, and 16)

iii. Screening neurological examinations for all 14 enrolled subjects (Subjects 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 13, 14, 15, and 16)

iv. Day 8 brief physical examinations for 11 subjects (Subjects 1, 2, 3, 4, 6, 8, 10, 11, 12, 13, and 14)

v. Follow-up Visit brief physical examinations for 8 subjects (Subjects 1, 2, 3, 6, 7, 8, 10, and 12)

b. On the following study records, your subinvestigator signed as having performed the respective study procedures. However, in fact, you or another study employee, not your subinvestigator, performed these study procedures:

i. Screening psychiatric evaluations for all 14 enrolled subjects (Subjects 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 13, 14, 15, and 16)

ii. Screening suicide risk assessment for 1 subject (Subject 15)

In the August 19, 2015, written response to the Form FDA 483, Mr. Lederman agreed that you had performed these procedures and had your subinvestigator's name added instead of your own. Mr. Lederman noted that the protocol did not specify to whom the responsibility of obtaining medical history and performing physical and neurological examinations could be delegated, nor did it specify that a licensed psychiatrist must document the psychiatric evaluations. In addition, Mr. Lederman stated that after your study staff collected the information to complete these study records, you and your subinvestigator carefully reviewed and discussed the eligibility of the subjects.

Mr. Lederman indicated further that the above-mentioned worksheets were case report forms that the sponsor did not provide. He noted that these study records were "merely considered a work in progress" and were never considered final documents.

This response is inadequate because, although the protocol did not specify to whom the responsibility of these study activities could be delegated, inaccurate information was recorded in numerous study records, which falsely attributed the conduct of study procedures to your subinvestigator.

In the conclusion of the written response, Mr. Lederman indicated that while you do not agree with the basis for the assertion of the deficiencies observed during the inspection, the responsibility for these deficiencies rests with your employer and not with you. We wish to emphasize that when you signed the Statement of the Investigator (Form FDA 1572) for the above-referenced clinical investigation, you agreed to take on the responsibilities of a clinical investigator at your site. Your explanation of these matters, when taken in conjunction with the violations described above, suggests systemic failures in your conduct of this clinical investigation. As a clinical investigator, it was ultimately your responsibility to ensure that these studies were conducted properly and in compliance with FDA regulations, both to protect the rights, safety, and welfare of study subjects and to ensure the integrity of study data.

Your failure to maintain adequate and accurate case histories, including the aforementioned discrepancies in the designation of the person who performed certain study procedures, raises concerns about the validity and integrity of the data captured at your site.

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

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol **(b)(4)** required you to ensure that study subjects met the protocol inclusion

and exclusion criteria before their enrollment. The investigational plan for Protocol **(b)(4)** required that you perform the **(b)(4)** approximately 24 hours after dosing. You failed to adhere to these requirements. Specifically:

a. For Protocol **(b)(4)**, you failed to ensure that study subjects met the protocol inclusion and exclusion criteria before their enrollment. Protocol **(b)(4)** specified that **(b)(4)**, confirmed by the Structured Clinical Interview for DSM-IV, Research Version, Patient Edition (SCID-RV/P), must be the primary psychiatric disorder present for the subject to be eligible for enrollment into the study. However, **(b)(4)** modules of the SCID were not completed at the screening visit for 13 subjects. Therefore, you failed to confirm a **(b)(4)** diagnosis as the primary psychiatric disorder using the SCID-RV/P for 13 of the 14 enrolled subjects.
Specifically:

i. For Subject 1, the **(b)(4)** module of the SCID was not completed at screening on October 16, 2014. A notation, "See **(b)(4)**," was recorded in its place. Subject 1 was randomized on November 13, 2014.

ii. For Subject 2, the SCID was administered at screening on October 20, 2014. However, only a portion of the Brief Description of the Traumatic Events List of the **(b)(4)** module was completed. Subject 2 was randomized on November 17, 2014.

iii. For Subject 3, the **(b)(4)** module of the SCID was not completed at screening on November 13, 2014. A notation, "See **(b)(4)**," was recorded in its place. Subject 3 was randomized on November 17, 2014.

iv. For Subject 6, the **(b)(4)** module of the SCID was not completed at screening on December 1, 2014. A notation, "See **(b)(4)**," was recorded in its place. Subject 6 was randomized on December 10, 2014.

v. For Subject 7, the **(b)(4)** module of the SCID was not completed at screening on December 11, 2014. Subject 7 was randomized on December 15, 2014.

vi. For Subject 8, the **(b)(4)** module of the SCID was not completed at screening on December 12, 2014. A notation, "See **(b)(4)**," was recorded in its place. Subject 8 was randomized on January 7, 2015.

vii. For Subject 10, the **(b)(4)** module of the SCID was not completed at screening on January 16, 2015. A notation, "See **(b)(4)**," was recorded in its place. Subject 10 was randomized on January 20, 2015.

viii. For Subject 11, the **(b)(4)** module of the SCID was not completed at screening on January 20, 2015. A notation, "See **(b)(4)**," was recorded in its place. Subject 11 was randomized on January 22, 2015.

ix. For Subject 12, the **(b)(4)** module of the SCID was not completed at screening on January 26, 2015. A notation, "See **(b)(4)**," was recorded in its

place. Subject 12 was randomized on February 2, 2015.

x. For Subject 13, the **(b)(4)** module of the SCID was not completed at screening (date not indicated). A notation, "See **(b)(4)**," was recorded in its place. Subject 13 was randomized on February 4, 2015.

xi. For Subject 14, the **(b)(4)** module of the SCID was not completed at screening on February 12, 2015. A notation, "See **(b)(4)**," was recorded in its place. Subject 14 was randomized on February 17, 2015.

xii. For Subject 15, the **(b)(4)** module of the SCID was not completed at screening on February 17, 2015. A notation, "See **(b)(4)**," was recorded in its place. Subject 15 was randomized on February 19, 2015.

xiii. For Subject 16, the **(b)(4)** module of the SCID was not completed at screening on February 25, 2015. A notation, "See **(b)(4)**," was recorded in its place. Subject 16 was randomized on March 4, 2015.

As described above, for 11 of the 13 subjects, a notation, "See **(b)(4)**," was recorded under the **(b)(4)** module of the SCID. We note that the protocol required the administration of both the SCID and the **(b)(4)** at screening, and that the protocol did not allow for the substitution of one assessment for the other. There was no explanation provided for the failure to perform the **(b)(4)** module of the SCID for 2 of the 13 subjects.

We also note that you used the Patient Version (SCID-I/P) of the SCID to administer the SCID for all enrolled subjects, rather than the Research Version (SCID-RV/P), as the protocol specified.

In the August 19, 2015, written response, Mr. Lederman agreed that the **(b)(4)** module of the SCID was not completed for these subjects. Mr. Lederman indicated that your study staff used the relevant information derived from the **(b)(4)** assessment to confirm diagnosis of **(b)(4)**, rather than using the information from the SCID. Mr. Lederman also stated that you knew all of the enrolled subjects from previous studies, for which SCID interviews were completed. In addition, Mr. Lederman noted that you were unaware at the time of the study that the SCID assessments for these subjects were not completed properly, and that this violation was not brought to your attention by either your study staff or sponsor monitors.

We wish to emphasize that as the clinical investigator, it was your ultimate responsibility to ensure that these studies were conducted properly and in compliance with FDA regulations, both to protect the rights, safety, and welfare of study subjects and to ensure the integrity of study data. Your response is inadequate because you did not indicate that you have put a corrective action plan in place to prevent similar violations in the future. Your explanation of these matters, when taken in conjunction with the violations described above, suggests systemic failures in your conduct of this clinical investigation.

Your lack of supervision and oversight of the clinical studies raises significant

concerns about the adequacy of your protection of study subjects enrolled at your site in the studies mentioned above, and also raises concerns about the integrity of the data generated at your site.

b. Protocol **(b)(4)** specified that subjects who participated in any other clinical study involving an investigational drug within 30 days or 5 half-lives (whichever is longer) before the current study begins and/or during study participation cannot be enrolled into this clinical investigation.

Subject 13 was previously enrolled in Protocol **(b)(4)** and completed the last study visit on January 20, 2015. However, this subject was randomized into Protocol **(b)(4)** on February 4, 2015, which is only 15 days after the last study visit for the previous study, and only 16 days from drug administration in the previous study.

In the August 19, 2015, written response, Mr. Lederman agreed that Subject 13 was enrolled in this clinical investigation within 30 days of participating in another clinical study. He noted that this subject did not report any adverse events in either of the clinical studies, and that he was closely monitored throughout the course of the study.

Your response is inadequate because you did not indicate that you have put a corrective action plan in place to prevent similar violations in the future. Your lack of supervision and oversight of the clinical studies raises significant concerns about the adequacy of your protection of study subjects enrolled at your site in the studies mentioned above, and also raises concerns about the integrity of the data generated at your site.

The eligibility criteria for each clinical investigation are designed to optimize the interpretability of the collected data and to minimize foreseeable harm to enrolled subjects. Enrollment of subjects who do not meet the eligibility criteria jeopardizes subject safety and welfare, and raises concerns about the validity and integrity of the data collected at your site. Particularly concerning to us is that you enrolled 13 of the 14 subjects into Protocol **(b)(4)** at your site without having ensured their subject eligibility.

c. Protocol **(b)(4)** required that the **(b)(4)** assessment be performed 24 hours post-dose at Visit 2 to assess the mood and well-being of the subjects, as well as to monitor them for adverse events. We note that the 24 hours post-dose **(b)(4)** assessment was also required as a secondary efficacy variable to measure the overall severity of **(b)(4)** symptoms.

You failed to perform the **(b)(4)** assessment at 24 hours post-dose for at least the following three subjects:

i. Subject 9 was administered study drug on February 3, 2015; however, the **(b)(4)** assessment was not conducted 24 hours post-dose at Visit 2.

ii. Subject 11 was administered study drug on February 10, 2015; however, the **(b)(4)** assessment was not conducted 24 hours post-dose at Visit 2.

iii. Subject 14 was administered study drug on March 3, 2015; however, the **(b)(4)** assessment was not conducted 24 hours post-dose at Visit 2.

In the August 19, 2015, written response, Mr. Lederman indicated that, given the protocol requirement for the **(b)(4)** to be administered twice within a short period of time (at 4 hours post-dose and at 24 hours post-dose), "the staff and subjects were instructed to rate these timeframes [*sic*] in their assessments."

Your response is inadequate because you did not indicate that you have put a corrective action plan in place to prevent similar violations in the future. Your lack of supervision and oversight of the clinical studies raises significant concerns about the adequacy of your protection of study subjects enrolled at your site in the studies mentioned above, and also raises concerns about the integrity of the data generated at your site.

As detailed above, you failed to conduct the investigation in accordance with the investigational plan. Specifically, your failure to adhere to protocol requirements for performing study procedures and your enrollment of subjects who did not meet eligibility criteria jeopardize subject safety and welfare, and raise concerns about the validity and integrity of the data collected at your site.

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 or will take to prevent similar violations in the future. Failure to address the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions, please contact Douglas Pham at 301-796-1955; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Douglas B. Pham, Pharm.D., J.D.
Acting Branch Chief
Compliance Enforcement Branch
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5348
10903 New Hampshire Avenue

Silver Spring, Maryland 20993

Sincerely yours,
{See appended electronic signature page}
David Burrow, Pharm.D., J.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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/s/

DAVID C BURROW
02/19/2016

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