U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Punjwani, Sohail S., M.D.

Department of Health and Human Services

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

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 10-HFD-45-01-04

Sohail Punjwani, M.D.
Professional Clinical Research
1065 NE 125th Street, Suite 221
North Miami, Florida 33161

Dear Dr. Punjwani:

Between January 20 and February 18, 2009, Ms. Brunilda Torres and Ms. Colleen Aspinwall, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of the following clinical investigations:

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

Protocol **(b)(4)**, entitled, "**(b)(4)**" of the investigational drug **(b)(4)** performed for **(b)(4)**.; and

Protocol **(b)(4)**, entitled "**(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, the documents submitted with that report, and your March 13, 2009 written response and its attachments, 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. Brunilda Torres and Ms. Colleen Aspinwall presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to conduct the studies or ensure they were conducted according to the investigational plans, and to protect the rights, safety and welfare of subjects [21 CFR 312.60].

a. Section 3 of Protocols **(b)(4)** specified that for subjects with a body weight less than 45 kg, the target dose of study drug was 60-80 mg/day; and for subjects with a body weight greater than or equal to 45 kg, the target dose of study drug was 120-160 mg/day. These protocols also specified that the dose level of 160 mg/day was not to be achieved before Day 8 of treatment. These study drug administration limits were not always followed.

The study drug and matching placebo were supplied as 20-, 40-, 60-, and 80-mg capsules, with the appearance and size slightly different among the dosage strengths. All medications were packaged in AM (morning dosing) and PM (evening dosing) blister cards that supplied medication for seven days plus three extra days. Each blister card was marked with four different-colored columns labeled with the letters A, B, C,

and D to distinguish the different potencies. Each column contained one potency (20-, 40-, 60-, and 80-mg), such that four capsule strengths were available for each dose. Per protocol, the nursing staff and subjects' parent(s) or guardian(s) were to select one capsule for the morning administration and one capsule for the afternoon administration, and leave the remaining capsules in the blister pack. Throughout the study and when dosing modifications were necessary, subjects were to receive clear specifications regarding which capsule was to be taken from the morning and afternoon blister cards. When changes to the original dosage plan were necessary, unscheduled visits were recommended so that subjects could be observed and so that changes to the dosage plan could be fully explained to the subjects and to his or her parent(s) or guardian(s).

Regarding Protocol (b)(4): Six of the seven randomized subjects received dosages in excess of protocol-specified limits:

i. Subject 1001, age 13 at the time of enrollment, was randomized on May 9, 2006, and discontinued on June 5, 2006, upon completion of the study. Subject 1001, with a documented weight of 46.8 kg, was overdosed on study medication for 20 consecutive days while participating in study **(b)(4)**.

Specifically, on May 16 and 17, 2006 (Treatment Days 8 and 9), this subject received 180 mg/day; on May 18 and 19, 2006 (Treatment Days 10 and 11), this subject received 240 mg/day; on May 20 and 21, 2006 (Treatment Days 12 and 13), this subject received 320 mg/day; on May 22, 2006 (Treatment Day 14), this subject received 400 mg/day; and from May 23 through June 4, 2006 (Treatment Days 15 through 27), this subject received 180 mg/day. This subject experienced sedation and dizziness during the study.

ii. Subject 1003, age 15 at the time of enrollment, was randomized on June 1, 2006, and discontinued on June 27, 2006, upon completion of the study. Subject 1003, with a documented weight of 65 kg, was overdosed on study medication for 21 consecutive days while participating in study **(b)(4)** Specifically, on June 7, 2006 (Treatment Day 7), this subject received 180 mg/day, in excess of the protocol-specified maximum dose of 160 mg/day prior to Day 8 of treatment. On June 8 and 9, 2006 (Treatment Days 8 and 9), this subject received 240 mg/day. From June 10 through 26, 2006 (Treatment Days 10 through 26), this subject received 400 mg/day. On June 27, 2006 (Treatment Day 27), this subject received 280 mg/day.

iii. Subject 1004, age 16 at the time of enrollment, was randomized on June 1, 2006, and discontinued on June 14, 2006, prior to study completion, due to lack of efficacy and sedation. Subject 1004 received doses in excess of the maximum target dose (160 mg/day) for 3 consecutive days while participating in Study **(b)(4)**. Specifically, on June 9, 2006 (Treatment Day 9), this subject received 320 mg/day. On June 10 and 11, 2006 (Treatment Days 10 and 11), this subject received 240 mg/day. This subject experienced sedation during the study.

iv. Subject 1005, age 15 at the time of enrollment, was randomized on June 14, 2006, and discontinued on July 18, 2006, prior to study completion, due to noncompliance. Subject 1005 received doses in excess of the maximum target dose (160 mg/day) for 16 consecutive days while participating in study **(b)(4)**. Specifically, on June 21 and 22, 2006 (Treatment Days 8 and 9), this subject received 180 mg/day. From June 23 through 27, 2006 (Treatment Days 10 through 14), this subject received 240 mg/day. From June 28 through July 3, and July 5 through July 6, 2006 (Treatment Days 15 through 20 and Days 22 through 23), this subject received 400 mg/day. On July 4, 2006 (Treatment Day 21), this subject received 200 mg/day.

v. Subject 1006, age 13 at the time of enrollment, was randomized on June 26, 2006, and discontinued on July 25, 2006, upon study completion. Subject 1006, with a documented weight less than 45 kg, was overdosed on study medication for a total of 7 consecutive days while participating in study **(b)(4)**. Specifically, from July 11 through 17, 2006 (Treatment Days 16 through 22), this subject received 400 mg/day.

vi. Subject 1007, age 10 at the time of enrollment, was randomized on June 27, 2006, and discontinued on July 25, 2006, upon study completion. Subject 1007, with a documented weight of 39.5 kg, was overdosed on study medication for 13 consecutive days while participating in study **(b)(4)** Specifically, from July 12 through 24, 2006 (Treatment Days 16 through 28), this subject received 120 mg/day.

Regarding Protocol (b)(4): The only subject randomized in this study received dosages in excess of protocol-specified limits:

vii. Subject 1001, an adolescent, was randomized on May 1, 2006, and discontinued on May 23, 2006, prior to study completion, due to worsening auditory hallucinations that apparently caused the subject to lacerate her wrists. Subject 1001, with a documented weight of 66.5 kg, was overdosed on study medication for 17 consecutive days while participating in study **(b)(4)**. Specifically, on May 5, 2006

(Treatment Day 5), this subject received 320 mg/day. From May 6 through 21, 2006 (Treatment Days 6 through 21), this subject received 400 mg/day.

In your March 13, 2009 response, you stated that you were first notified on July 26, 2006 by **(b)(4)** data management personnel that there were dosing errors in the conduct of the studies, stemming from your mistaken assumption that all capsules contained in the study drug blister pack were of the same 20 mg strength. Immediately upon becoming aware of this issue, you stated that you telephoned each subject's parent or guardian to inform him or her of this error, and inquired about any possible safety concerns or issues, of which there were none. You stated that during these calls, you instructed the parents and guardians to stop dispensing the currently prescribed dosage and begin the corrected dosage amount. A follow-up letter was also sent to the parents and guardians on August 4, 2006. You noted that the **(b)(4)** study monitor conducted a targeted review with you and your research staff on the correct dosing and dispensing of study medication on July 26, 2006. Additionally, on July 31, 2006, your research staff attended the **(b)(4)**-hosted Question and Answer **(b)(4)** Recruitment meeting that included training on the dosing and dispensing for all **(b)(4)** research sites conducting the above-referenced studies in which you were involved.

As part of your corrective action plan, you made formal revisions to your Standard Operating Procedures (SOPs). Specifically, you indicated that the Dosing and Dispensing of Investigational Product SOP was revised to add a more detailed inpatient and outpatient dosing process and to further specify how the clinical investigator, or designee, should document dosing instructions in both milligrams and tablets/capsules, as well as clearly document original dosing schematics and any titration throughout the study. You also noted that the Study Launch Procedures SOPs were revised to: (1) emphasize the materials reviewed and received at the investigator meetings, (2) include the review of the applicable Institutional Review Board (IRB) manuals for investigators, and (3) include internal documentation of the dosing and procedures to be performed on a mock subject from screening through study completion. Additionally, you stated that the Quality Assurance/Quality Control (QA/QC) Program SOP was also revised to ensure the oversight of two subjects, or 10% of the population randomized, with ongoing review of dosing and dispensing, protocol compliance, prior/concomitant medications, and prohibited medications.

We acknowledge your response. However, we are concerned that the response is not adequate to prevent future recurrence of the violation noted above. In particular, we are concerned that you did not properly understand the study drug packaging from the start of the study and you did not ensure that the appropriate dose was administered throughout the study. We are aware that the sponsor subsequently changed the packaging for the investigational product following observations that clinical investigators were not properly dosing subjects. Notwithstanding the packaging concerns, as clinical investigator, you retain responsibility for ensuring that the protocol is followed, including ensuring that the proper dose is administered to subjects.

b. Section 5.3.3 of Protocols **(b)(4)** and **(b)(4)** specified that you were to have developed a titration plan to increase the subject's total daily dose of study medication from a 20 mg starting dose (at the baseline visit) to a target dose achieved over 2 weeks, in general. In developing the titration plan, you were to have considered the subject’s psychiatric history, current psychiatric status, and weight. The Protocol also permitted you to modify the plan at any time based on a subject’s clinical response and toleration. You or a staff member were to have explained the titration plans to subjects, and to have clearly specified which capsules the subjects were to have taken from each AM and PM column for the first seven days of the titration plan. Furthermore, Section 5.3.4 of Protocols **(b)(4)** and **(b)(4)** specified that you were to have assessed subjects' compliance with study medication administration at Week 1 and at each subsequent visit. Additionally, you were to have counted medication returned by subjects to reconcile medication dispensed with subjects' reported usage. There is no evidence that you developed dosing titration plans for the subjects enrolled in these studies, or that you assessed subjects' compliance and performed the requisite drug reconciliation as specified in the protocols.

In your March 13, 2009 response, you acknowledged your failure to fully document specific dosing instructions and titration plans. You stated that you recognized that this specific documentation was necessary in order to ensure accurate dosing. As a corrective measure, you stated that your Dosing and Dispensing of Investigational Product SOP will be revised to include more specific information on how, why, and when dosing changes are documented. We acknowledge your assurance that corrective actions will be taken. However, we note that your response did not contain a detailed outline of procedures or processes that would be implemented to prevent future recurrence of the violation noted above. Specifically, we are concerned that your lack of adherence to the protocol in developing dosing titration plans, assessing subjects' compliance, and performing drug reconciliation led to the significant overdoses and resultant adverse events experienced by the pediatric subjects enrolled at your site as described above. As you noted in your response, you were first notified on July 26, 2006 by **(b)(4)** data management personnel that there were dosing errors in your conduct of these pediatric studies. It is likely that your lack of adherence to the protocols led to your failure to recognize the overdosing at your site, until it was discovered and brought to

your attention by the sponsor's data management unit. While there may have been concerns with the packaging of the study drug, your failure to conduct the requisite safety measures contributed to the unnecessary exposure of pediatric subjects to significant overdoses, which jeopardized the subjects' rights, safety, and welfare.

c. Section 6.2 of Protocol **(b)(4)** required serum pregnancy and urine drug screening tests to be performed at baseline. These tests were not performed for the following subjects:

i. Subject 1002's serum pregnancy and urine drug-screening tests were not performed at baseline.
ii. Subject 1003's serum pregnancy and urine drug-screening tests were not performed at baseline.
iii. Subject 1004's urine drug-screening tests were not performed at baseline.
iv. Subject 1007's urine drug-screening tests were not performed at baseline.

In your March 13, 2009 response, you stated that Subjects 1002, 1003, 1004, and 1007 were inpatients at baseline. Given that the pregnancy and urine drug screen tests were negative for these subjects at the time of screening, you indicated that your research staff did not repeat the tests at baseline as they assumed there was no opportunity for the results to change. You noted that a Visit Checklist was created to ensure that all study-related procedures are being conducted for each visit, and that completion of this checklist is now standard work practice at your site. We acknowledge your response. However, regardless of the results obtained at screening, the serum pregnancy and urine drug tests should also have been performed at baseline as specified in the protocol. The Visit Checklist you have instituted as standard practice at your site to prevent any similar future occurrences is acceptable.

2. You failed to promptly report to the Institutional Review Board (IRB) all changes in the research activity [21 CFR 312.66].

On August 2, 2006, upon confirming study drug dosing errors, the sponsor instructed you to cease subject enrollment at your site. On February 7, 2007, the sponsor notified you of its decision to terminate your investigational site's participation in the **(b)(4)** pediatric studies, including Protocols **(b)(4)** due to good clinical practice (GCP) noncompliance related to dosing errors and continued delays in resolution of queries and data-clarification forms. You failed to notify the IRB of these decisions made by the sponsor. Documentation available at your site indicates that notification of the IRB was limited to the submission of protocol deviation reports concerning subjects' overdosing errors. Furthermore, you failed to notify the IRB of the sponsor's decisions in the continuing review reports and study close-out letters.

In your March 13, 2009 response, you stated that you assume full responsibility for the lack of notification to the IRB. To ensure continued compliance with IRB guidelines, you noted that formal training concerning IRBs was conducted at your site on March 17, 2007, and the Western Institutional Review Board Guide for Researchers Versions 1.5 and 1.6 was distributed at your site for independent review. We acknowledge your response and find your corrective actions acceptable.

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 Cullity (formerly 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:

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Sincerely yours,
/S/

Leslie K. Ball, M.D.
Director
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