DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Eugene Lu, MD
Arkansas Pediatric Clinic
500 South University Avenue, Suite 200
Little Rock, AR 72205

Dear Dr. Lu:

Between May 12 and 21, 2009, Mr. Joel Martinez and Ms. Tracy Washington, 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).

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.

At the conclusion of the inspection, Mr. Martinez and Ms. Washington presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We have reviewed the inspection report, the documents submitted with that report, and your written response to the Form FDA 483 dated June 1, 2009. We do not find your response to be acceptable in addressing the matters under complaint, which are described below.

Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products as published under Title 21, Code of Federal Regulations (CFR), part 312.70 (copy enclosed).

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR 312.70.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].**

   When you signed the Statement of Investigator (Form FDA 1572) for the above-referenced clinical trial, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trial is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60]. By signing Form FDA 1572, you specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and that these trials were conducted in a manner that protects the rights, safety, and welfare of human subjects.

   We note that your failure to adequately supervise this study led to significant problems with the conduct of the study, including the submission of false information to the sponsor in a required report as described below. You stated in your June 1, 2009, response to Form 483 that many of the detailed findings were mistakes made by your study coordinator and that if you had supervised her work more closely, perhaps that would have prevented the repetition of several errors.

2. **You repeatedly or deliberately submitted false information to the sponsor in a required report [21 CFR 312.70].**

   According to the protocol, "(b) (4) symptoms will be assessed, with the help of the parent/guardian/caregiver of the subject, for 7 days before randomization and on the morning of Visit 3… Symptoms will be evaluated at Visit 3 to meet the inclusion criterion before randomization into the study. The symptom criterion is satisfied when the daily AM instantaneous total (b) (4) symptom score is ≥ 4 on any 4 out of the last 7 consecutive days immediately prior to and including the morning of Visit 3., Instantaneous (at the moment) (b) (4) symptoms ((b) (4)) will be

assessed upon arising in the morning (AM) according to the following scale and recorded on the daily symptom diary:

0 = symptom absent
1 = mild (present but not annoying to self)
2 = moderate (present and annoying to self but does not interfere with sleep or daily living)
3 = severe (interferes with/or unable to carry out activities of daily living or sleep)"

Our inspection revealed the following:

a. For subjects 002 and 005, diary scores were falsified. Specifically, our inspection revealed that scores were changed after the subjects' diaries had been submitted to you and without permission from or knowledge of the subjects' parents.

b. Case report forms and diaries reviewed during the inspection also indicated that for subjects 002, 005, 007 and 017, changes were made to Visit 3 diary instantaneous scores. These changes appear to reflect false information in that they were made after the subjects' diaries had been submitted by the subjects' parents containing scores that did not meet eligibility criteria. The changes resulted in subjects 002, 005, 007, and 017 meeting inclusion criteria for randomization. We note that these four subjects were the only subjects randomized in the clinical investigation.

We further note that you subsequently submitted the above false information to the sponsor in a required report.

We acknowledge your response to the FDA Form 483, in which you stated that your study coordinator was responsible for changing these diary data. Additionally, we note your statement that you placed the study coordinator on a 30-day probationary period following the sponsor's audit of this study during which time all study procedures and documentation were closely observed and reviewed by the department manager and you. You also stated that at the end of this time, the study coordinator was taken off probationary status and her work continued to be closely monitored. You further stated that shortly before being notified of the FDA audit that was to be conducted on Protocol (b) (4), the decision was made to terminate the study coordinator after receiving information from her previous employer alleging similar findings during an FDA audit of work done by her at their site. The study coordinator submitted a letter of resignation and her last day of employment at Arkansas Pediatric Clinic was May 22, 2009.

Your affidavit states that you were unaware of your study coordinator's changing the instantaneous scores, and that you did not instruct her to do so. Furthermore, we also acknowledge the corrective actions that you have reportedly taken to prevent protocol violations on the part of study staff in the future: A Standard of Practice has been established in order to specify expected procedures for correcting mistakes, directing parents on completion of diary cards, and making changes on source documents at the

advice of the "CRA". However, you have failed to address how you, personally, will ensure that a similar violation does not recur in your conduct of FDA-regulated clinical research in the future.

3. You failed to conduct the studies or ensure they were conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60].

a. The protocol inclusion criteria state that the subject must be "[s]ymptomatic (daily AM instantaneous total (b) (4) symptom score is ≥ 4) on any 4 out of the last 7 consecutive days immediately prior to and including the morning of Visit 3." This information was captured in each subject's diary. Since you stated in your affidavit that you do not recall reviewing the diary data, you failed to ensure that Subjects 002, 005, 007, and 017 met this inclusion criterion. In addition, we note that as discussed above the data indicating that your subjects met the eligibility criteria was falsified.

b. You failed to ensure that your study coordinator was trained in the use of the Stadiometer to properly obtain the protocol-required recording of three height measurements at various time points throughout the study, as evidenced by the height measurements for Subject 002, which indicate that the subject shrank during the time period from Visit 1 to Visit 4 (see number 5 below). In addition, an additional two height measurements were required to be taken if the difference among the triplicate readings was greater than or equal to 0.4 cm. Despite height measurement differences of greater than or equal to 0.4 cm, additional two height measurements were not taken as required for the following subjects at screening Visit 1: Subjects 002, 004, 006, 010, and 013.

c. You failed to ensure that your study coordinator, to whom you delegated the responsibility of reviewing the completed diaries with the subjects' parents, understood that an intensity rating scale score of "4" was not a possible score for subject 0002, because as noted above in item 2, the options for each symptom intensity score are zero to three.

Your written response states that "too much latitude was given to the study coordinator" to follow the investigational plan. We also acknowledge that you have described corrective actions that include Standard of Practice procedures for determination of eligibility and documentation in addition to your statement indicating that you will personally dedicate more of your time to inclusion/exclusion criteria, the oversight of study procedures, the activities of your study coordinators, and protocol training in the future. However, your written response did not address corrective actions to ensure how you will provide oversight of study procedures, activities of the study coordinators, and protocol training for you and your staff to ensure that a similar violation does not recur in your conduct of FDA-regulated clinical research in the future.

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

   FDA regulations state that an investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. You did not maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, for (b) (4).

   a. The Visit 8 source document worksheet does not show the number of bottles of investigational drug collected for Subjects 002 and 0017. The source document worksheets should have reflected the collection of the 2 bottles that were dispensed at Visit 7 for these subjects.

   b. The Visit 3 source document worksheet shows that 2 bottles of rescue medication were collected during the visit for Subject 002. However, the Visit 2 worksheet documents that one bottle was collected and only one bottle was dispensed. Therefore, either the Visit 2 or Visit 3 worksheet is incorrect.

   c. The early termination source document worksheet does not show the number of bottles of rescue medication collected for Subject 005. The early termination source document worksheet should have reflected the collection of the one bottle that was dispensed during the previous Visit 8.

   We note your acknowledgment in your written response that the repetition of several errors in the conduct of the clinical investigation may have been prevented if you had supervised the study coordinator more closely. However, your written response did not address corrective actions to ensure accurate and adequate drug accountability in the future.

5. **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)].**

   The protocol study schedule requires triplicate Stadiometer height measurements at each visit; these measurements were the primary efficacy endpoint for the study. Height measurements for Subject 002 were recorded at multiple visits and subsequently were changed months later without documenting the rationale for the change. For example:

   a. Initial Visit 1 height measurements of 1080 mm, 1084 mm, and 1081 mm were taken on May 31, 2007. These measurements were then changed to l068 mm, 1068 mm, 1068 mm, respectively, on October 30, 2007 without explanation.

   b. Initial Visit 4 height measurements of 1070 mm, 1070 mm, 1070 mm were taken on October 30, 2007, but were changed on February 12, 2008, to 1170 mm, 1170 mm, and 1170 mm, respectively, without explanation.

c. Visit 6 height measurements taken on January 29, 2008, were 1159 mm, 1160 mm, and 1160 mm, indicating that Subject 002 was shorter than s/he was on prior visits.

We note your acknowledgment in your written response that the repetition of several errors in the conduct of the clinical investigation may have been prevented if you had supervised the study coordinator more closely. We also acknowledge that you have described corrective actions indicating that you will personally dedicate more of your time to the oversight of study procedures, the activities of your study coordinators, and protocol training in the future. However, your written response did not address corrective actions to ensure how you will provide oversight of study procedures, activities of the study coordinators, and protocol training for you and your staff to ensure that a similar violation does not recur in your conduct of FDA-regulated clinical research in the future.

6. You failed to obtain informed consent 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]. In seeking informed consent, the FDA regulations require that certain information, including a description of any reasonably foreseeable risks to the subject, must be provided to each subject [21 CFR 50.25].

You failed to obtain legally effective informed consent from subjects to whom you distributed the investigational new drug (b) (4). The informed consent documents presented to the parent/legal guardian of Subjects 0006, 0008, 0009, 0010, 0013, and 0016 were missing pages 5 and 7. Because these subjects' parents/legal guardians were not given the opportunity to sign the complete informed consent documents, which contained information related to Study Treatment Procedures for Visits 10 and 11, Unforeseen Risks, Potential Benefits, New Findings, Alternative Methods of Treatment, and Compensation for Participation, they did not have sufficient opportunity to consider whether or not to participate in the study as required by 21 CFR 50.20.

We note that in your written response you have explained that you have revised your Standard of Practice process for obtaining informed consent from subjects by requiring that two clinical research coordinators review the informed consent form before the parent leaves the office. However, you have not addressed how you will personally ensure that a similar violation does not recur in your conduct of FDA-regulated clinical research in the future.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational products. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above-listed violations, FDA asserts that you have failed to protect the rights, safety, and welfare of subjects under your care, repeatedly or deliberately submitted false information to the sponsor; and repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks to human subjects and jeopardized the integrity of data; and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above-stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at 301-796-3150 to arrange a conference time or to indicate your intent to respond in writing.

Should you choose to respond in writing, your written response should be forwarded within thirty (30) days of receipt of this letter.

Your reply should be sent to:

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5342
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and a representative of your choice may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The FDA's Center for Drug Evaluation and Research (the Center) will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will

provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products.

You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

To enter into the enclosed consent agreement with FDA, thereby terminating this disqualification process, you must:

(1) initial and date each page of this Agreement;
(2) sign and date the last page of this Agreement; and
(3) return this Agreement initialed, signed and dated to the signature below.

A copy of the fully executed Agreement will be mailed to you.

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
Food and Drug Administration

Enclosures:
#1 - Consent Agreement
#2 - 21 CFR 312.70
#3 - 21 CFR 16
#4 – 21 CFR 312.60
#5 – 21 CFR 312.62

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
03/16/2010