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

Francisco J. Candal, M.D.
Northshore Research Association
2240 Gause Boulevard, East
Slidell, LA 70461

Dear Dr. Candal:

Between October 27, 2008, and November 14, 2008, Ms. Dana Daigle and Ms. Barbara Wright, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations:

> Protocol BY217/M2-124, titled "Effect of roflumilast on exacerbation rate in patients with COPD. A 52 week, double-blind study with 500 mcg roflumilast once daily versus placebo," of the investigational drug roflumilast, performed for Altana Pharma; and
>
> Protocol D5899C00001, titled "A 12-Month Double-blind, Double-dummy, Randomized, Parallel group, Multicenter Efficacy and Safety Study of SYMBICORT® pMDI 2 x 160/4.5 µg bid and 2 x 80/4.5 µg bid Compared to Formoterol TBH 2 x 4.5 µg bid and Placebo in Patients with COPD," of the investigational drug Symbicort®, performed for AstraZeneca.

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research 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, Ms. Daigle and Ms. Wright presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We have reviewed the inspection report and the documents submitted with that report. We note that you have not provided a written response to the Form FDA 483. We do not find

your verbal responses to FDA investigators 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 informed consent and the proper conduct of clinical studies involving investigational products, as published under Title 21, Code of Federal Regulations (CFR), part 312 (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 personally conduct or adequately supervise the clinical investigations [21 CFR 312.60].**

   When you signed the Statement of Investigator (Form FDA 1572) for Protocol BY217/M2-124, 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 in a manner that protects the rights, safety, and welfare of human subjects.

   Specifically, you failed to adequately supervise the study coordinator to whom you delegated tasks. Your failure to adequately supervise the study coordinator led to the significant problems with the conduct of the study that are described below.

   You stated during the inspection that you thought the role of the study monitor is to ensure that the study is conducted within the guidelines set by the sponsor. You further stated that the problems could have been solved earlier if the monitor had monitored the study prior to six months into the study. We find your response unacceptable. As the clinical investigator, it is your responsibility to supervise the conduct of the study. This responsibility may not be delegated to the study monitor.

2. You failed to obtain informed consent of subjects as required under 21 CFR 312.60.

For Protocol BY217/M2-124, our investigation found that the signature of Subject 88109 was forged on the IRB-approved revised consent form with the version date of February 20, 2007.[1] On November 16, 2009, FDA investigators showed Subject 88109 a consent form with the version date of February 20, 2007, and with the subject's signature date of April 9, 2007, and asked the subject if the signature on the consent form was the subject's. Subject 88109 stated that the signature on that consent form was not the subject's signature. We conclude that the signature of Subject 88109 on the above-referenced consent form was forged.

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

Protocol BY217/M2-124 states: "Pre- and post-bronchodilator measurements will be performed at all visits. Directly after the pre-bronchodilator measurement the patient will inhale 4 puffs of salbutamol/albuterol (360 mcg salbutamol/albuterol base ex mouthpiece) from an MDI with a spacer, and lung function measurement is to be repeated after 30 min (± 15 min). After the post-bronchodilator test the patient will be asked to take his/her study medication."

a. Our investigation found that these pulmonary function tests (PFTs) were either not conducted, or were not conducted at the required times, for 9 of 11 subjects enrolled. Specifically:

   i. Visit 6 PFTs were not conducted for Subject 88405.
   ii. Subject 88111's end-of-study post-bronchodilator test was conducted only 5 minutes after the pre-bronchodilator measurement.
   iii. The end of study PFTs were not conducted for Subjects 88109, 88112, 88116, 88402, 88403, 88404, and 88405.
   iv. Subjects 88111, 88112, 88116, 88403, and 88472 inhaled Ventolin® (albuterol sulfate) prior to the "pre-bronchodilator" measurement. The pre-bronchodilator PFT should have been conducted before the subject received a bronchodilator such as Ventolin®.

b. The protocol required certain laboratory assessments to be conducted at Visit 0, Visit 7, and the end-of-study visit. Our investigation found that Subjects 88402, 88405, and 88472 were randomized without the required assessments.

[1] An IRB Notification Form (dated July 2, 2007) discovered during the inspection indicated that the signatures of Subjects 88116, 88403, and 88472 were forged by the study coordinator. You were asked about these signatures during the inspection. You explained that your study coordinator adamantly denied forging subjects' signatures on the consent forms, but you stated that when the monitor brought this to your attention, you terminated your study coordinator.

i. Subject 88402 was enrolled on Saturday, February 10, 2007, Visit 0. Because the blood draw was on a weekend, the blood specimen was beyond stability and was therefore deleted. The subject's Visit 1 occurred on February 24, 2007, and Visit 2 occurred on March 10, 2007; however, the blood specimen was not redrawn until Monday, April 9, 2007.

ii. Subject 88405 was enrolled on February 16, 2007. The Visit 0 laboratory report documents that the chemistry and endocrinology specimens were "centrifuged inadequately at site, tests deleted." There was no documentation to show that these tests were repeated.

iii. Subject 88472 was enrolled on March 2, 2007. The Visit 0 laboratory report documents that the endocrinology specimens were "centrifuged inadequately at site, tests deleted." There was no documentation to show that these tests were repeated until June 22, 2007. This was the subject's end-of-study visit due to the subject's withdrawal of consent.

c. The protocol required the investigator to "regularly monitor" the well-being of each study subject via multiple phone contacts to ensure subject safety during the study. Specifically, during the telephone calls, the investigator was to ask the subject whether he/she experienced a deterioration of his/her disease, and whether any additional COPD medication had been administered. Additionally, the investigator was to ask the subject if he/she experienced any other adverse event. The outcome/findings of the telephone interviews were to be documented in the subjects' source data. Our investigation found that all telephone interviews were documented as having been conducted by the study coordinators, rather than by you, the clinical investigator, as required by the protocol. You admitted to the FDA investigators that you did not conduct any of these telephone interviews, and you denied knowing that you were responsible for this study task.

4. 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)].

Protocol BY217/M2-124

a. The source documents for all 11 subjects enrolled did not document the subjects' medical histories to show that the subjects had chronic productive cough for 3 months in each of the 2 years prior to baseline visits, as required by the protocol.

b. The case report forms (CRFs) for baseline visits for at least six subjects (88109, 88112, 88116, 88402, 88403, and 88404) document that the Hemoccult (guaiac) test required by the protocol was performed; however, study records contain notes indicating that the subjects denied or could not recall that this test was performed.

c. According to the IRB Notification Form dated July 2, 2007,[2] the study coordinator forged your signature on the data query forms, backdated source notes, fabricated source documents to show telephone calls with subjects that did not occur, and fabricated case histories to show that Hemoccult tests were done when, in fact, the tests were not performed.

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d. Source documents were not available to support the entries made in the case report forms (CRFs) for all 12 subjects enrolled in this study. Specifically, the only records available in the study binders to support inclusion of subjects were checkmarks in source document templates completed during verbal interviews with the prospective subjects. Clinic records from you or from other treating physicians were not available to document the subjects' medical histories to show that subjects met inclusion criteria, and to document the data entered into the CRFs.

During the inspection, you explained to the FDA investigators that subjects' records documenting their past medical histories were lost during Hurricane Katrina. We acknowledge your explanation; however, you failed to document your attempts to retrieve subjects' medical histories to support their inclusion into the study.

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; and that you 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.

[2] Our inspection found no evidence, i.e., no facsimile confirmations or acknowledgements for receipt of these reports from the IRB, in the regulatory files. The site's IRB correspondence file contains IRB acknowledgment or receipt of only one Protocol Deviation Report that was submitted to the IRB on April 10, 2007.

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 with 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 signer 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 16
#3 – 21 CFR 50
#4 – 21 CFR 56
#5 – 21 CFR 312.60
#6 - 21 CFR 312.70

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
03/02/2011