



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

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ghandi M. Saadeh, M.D.
850 Kempsville Road
Sentara Medical Group, Clinical Research
Norfolk, VA 23502

Ref: 10-HFD-45-12-02

Dear Dr. Saadeh:

Between December 8, 2008, and February 4, 2009, Mr. Stephen C. Eason, 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)
performed for (b) (4);

Protocol (b) (4) entitled (b) (4)
performed for (b) (4); and

Protocol (b) (4) entitled (b) (4)
performed for (b) (4).

This inspection is a part of 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 the study have been protected.

At the conclusion of the inspection, Mr. Stephen C. Eason 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, and note that you have not provided a written response to the Form FDA 483.

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 (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.

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

1. You submitted false information to the sponsor in a required report [21 CFR 312.70(a)].

In the (b) (4) study, the case histories for Subjects 225 and 222 contained photocopies of insulin study subject diaries that were not completed by the study subjects.

FDA's investigation revealed that Subject 225 was never provided with a study diary to complete, nor was he administered any study medication.

FDA's investigation revealed that study diaries purported to be completed by Subject 222 from 10/13/07 to 12/19/07 and 12/21/07 to 1/12/08 were not the diaries that he had completed for the study.

According to the protocol, the 4 most recent fasting blood glucose (FBG) values and pre-evening meal blood glucose (BG) values were to be transferred to the electronic case report form (eCRF) at each office visit. In addition, subjects were to complete 7-point self-monitored blood glucose (SMBG) profiles on 3 separate days in the 2-week period prior to Visits 3, 6, and 9. Data from the 7-point SMBG profiles were to be transferred to the eCRF at Visits 3, 6, and 9. In the case of early discontinuation, as many applicable 7-point SMBG values from the patient's study diary were to be entered into the eCRF as were available. The eCRF data derived from the insulin study subject diaries were used to evaluate at least 2 secondary objectives of the study. eCRF data for Subjects 225 and 222 were based on insulin study subject diaries which were not completed by the study subjects.

2. You failed to prepare and maintain adequate and accurate case histories that record all observations and 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)].

- a. In the (b) (4) study, laboratory results collected on October 15, 2007 for Subject 225 show evidence of alteration. Our investigator found two versions of the lab results, one with the HbA1c result and one without the HbA1c result. Both versions look very similar below the line indicating “Chemistry,” including the handwritten statement, “liver, kidney tests are fine,” and the signature and stamp of your subinvestigator, (b) (6), M.D. In the version without the HbA1c result, above the line indicating “Chemistry” there is a faint line, which suggests that the lab results were altered. The inclusion criteria described in the study protocol stated that subjects must have $HbA1c \geq 7.5\%$. The version of the lab result which includes HbA1c shows HbA1c of 6.2.
- b. In the (b) (4) study, original insulin study diaries were missing for Subject 222, Subject 224, Subject 225, Subject 226, and Subject 227.
- c. In the (b) (4) study, several progress notes for subject # 225 for Visit 1 are inconsistent with the laboratory report and laboratory requisition form. According to the progress notes, the subject returned on October 25, 2007, to have labs drawn. However, according to the laboratory report and laboratory requisition form, the labs were drawn on October 24, 2007.

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

- a. In the (b) (4) study, the protocol specified that from the Week 12 visit through the end-of-treatment visit, a randomized subject who had an HbA1c result of $\geq 8.5\%$ and $\leq 0.5\%$ reduction in HbA1c as compared with the baseline HbA1c, was to have the HbA1c result confirmed by a second sample drawn within 5 days after the first sample. Upon confirmation of the original results, the subject was to be rescued and an early termination visit was to be completed. In a September 8, 2008 memo to file, Dr. Saadeh explained that Subject 2501 was not rescued according to the protocol. According to the September 8, 2008 memo, at Week 12 (June 13, 2007) and Week 16 (July 11, 2007), Subject 2501 had HbA1c results of 9.4% and 9.6%, respectively, but was not rescued in accordance with the protocol. A second sample was not drawn after either visit, and the subject did not complete an early termination visit due to the rescue criteria’s being met.
- b. In the (b) (4) study, the protocol specified that subjects were to receive less than 7 days of any antidiabetic therapy within 3 months prior to screening. Subject 2504 was enrolled on May 1, 2007. Subject 2504 was prescribed (b) (4) in August 2005. Although there is no documentation with regard to the date on which subject 2504 stopped taking (b) (4) she was randomized on June 12, 2007. The subject later

stated that she stopped taking diabetic medications for 4-5 weeks prior to being enrolled in the study.

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

- a. In the (b) (4) study, your Patient Study Drug Accountability Log, is incomplete. For example, no data was entered in the “Amount Dispensed” column, and the fifth row of data contains only the visit number and the subject number.
- b. In the (b) (4) study, five cartridges of investigational study drug (Lot# (b) (4)) and one prefilled investigational study drug administration pen (Lot# (b) (4)) were unaccounted for.

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.

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 proceeding, 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CONSTANCE LEWIN
01/04/2010

LESLIE K BALL
01/04/2010