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

Thomas Mendolia, D.O.
Northwest Piedmont Clinical Research
4155 Winding Oaks Trail
Lewisville, NC 27023

Dear Dr. Mendolia:

Between October 18, 2010, and November 1, 2010, Ms. Eileen Bannerman, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations of the investigational drug (b) (4), performed for (b) (4).:

- Protocol (b) (4) (originally dated November 28, 2007; Amendment 1 dated March 24, 2008; and Amendment 2 dated January 6, 2009), titled (b) (4) ; and
- Protocol (b) (4) (originally dated November 28, 2007; Amendment 1 dated March 24, 2008), titled (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 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. Bannerman 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 did not provide 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 312.70 (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 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 plans for Protocols (b) (4) and (b) (4) required, among other things, that you enroll subjects who meet inclusion criteria, that you do not enroll subjects who meet exclusion criteria, and that you perform physical examinations and certain assessments, such as an assessment of symptoms and assessment of serum gastrin levels. You failed to adhere to these requirements. Specifically:

a. Section 9.2, Inclusion Criteria, of the protocols referenced above states: "Each subject must meet the following criteria to be enrolled in this study … Subjects who are H. Pylori negative based on the UBT [Urea Breath Test]."

The following subjects were enrolled but did not meet the inclusion criteria as described above:

i. Subject 1106 had a UBT sample collected on June 9, 2008. Subject 1106 was randomized into Protocol (b) (4) on June 20, 2008, before the availability of and your review of the UBT lab report. The laboratory report with a positive UBT result was dated July 1, 2008, and the results were reviewed on July 3, 2008.

ii. Subject 1137 had a UBT sample collected on July 11, 2008. The positive laboratory report was dated July 25, 2008. The results were reviewed on July 28, 2008. Despite having a positive UBT, Subject 1137 was randomized into Protocol (b) (4) on August 8, 2008.

b. Section 9.3, Exclusion Criteria, of the protocols states: "Subjects who meet any of the following criteria will be excluded from the study: … Current or a history of Barrett's esophagus.… Subjects with clinically relevant abnormal laboratory tests at the screening visit, including liver enzymes greater than 2 times the upper limit of normal.… Active alcohol and substance abuse…."

The following subjects were enrolled but met the exclusion criteria as described above:

i. Subject 1184 had a liver enzyme test, ALT, collected on August 19, 2008, at Visit 1, Day -28. The reference range for the ALT is 10-40 U/L. The laboratory result for Subject 1184 was reported to be 88 U/L more than 2 times the upper limit, on August 20, 2008. The report was reviewed on August 25, 2008. Despite having an exclusionary ALT level, Subject 1184 was randomized into Protocol (b) (4) on September 3, 2008.

ii. Subject 1195 had a previous history of Barrett's esophagus dating back to at least 2003, based on records available in the research chart, including a previous endoscopy that you performed in 2006. Subject 1195 signed an informed consent document for Protocol (b) (4) on August 25, 2008; underwent screening visits from August 25 to August 27, 2008; and was enrolled and dispensed investigational product on September 5, 2008, despite having met the exclusionary criterion of a history of Barrett's esophagus.

iii. Subject 1015 had a history of alcohol abuse beginning in 1994 with no end date, as noted on the Medical History page of the Visit 1 (March 19, 2008) Case Report Form (CRF). This subject was randomized into Protocol (b) (4) on April 16, 2008, despite appearing to meet the exclusionary criterion of active alcohol abuse.

c. Section 2.1, Protocol Flowchart, and Section 12, Schedule of Assessments for Protocols (b) (4) and (b) (4), outline the assessments to be performed at each visit.

Our inspection found that you did not perform required assessments for the following subjects:

Subject Protocol (b) (4)	**Visit 1 Missing assessments**	**Visit 2 Missing assessments**	**Visit 3 Missing assessments**	**Visit 4 Missing assessments**	**Visit 6 Missing assessments**
1110			6/23/08 VS		
1120	6/16/08 PE, MH	6/20/08 SG		7/30/08 VS, IA, ECG, SG, blood/urine	8/14/08 VS, PE
Subject Protocol (b) (4)	**Visit 1 Missing assessments**	**Visit 2 Missing assessments**	**Visit 3 Missing assessments**	**Visit 4 Missing assessments**	**Visit 6 Missing assessments**
1181				9/29/08 blood/urine	
1107			7/3/08 IA	7/31/08 ECG	

VS = Vital signs; MH = Medical History; IA = Investigator assessment of symptoms; SG = serum gastrin sample; PE = Physical exam; ECG = electrocardiogram; blood = laboratory tests; urine = urinalysis

Enrollment of subjects who do not meet eligibility criteria and failure to perform protocol-required assessments jeopardize the safety and welfare of the subjects under your care and raise concerns about the validity and integrity of the data collected at your site.

2. 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 source documents and CRFs. Furthermore, Section 17.6 of the protocols referenced above states: " … CRFs must accurately reflect data contained in subject's records (e.g., source documents)." You have failed to maintain adequate and accurate case histories that contain all source documents and that accurately reflect data contained in source documents. Examples of this failure include the following:

a. Our investigation found many discrepancies between the source documents and the information reported in the CRFs. Specifically:

Protocol (b) (4) Subject	Source Document	CRF
1002	UBT recorded as 3/31/08	UBT recorded as 3/17/08
	ECG 5/12/08 reported as abnormal	ECG 5/12/08 recorded as normal
1106	EGD printout 6/17/08 reported as Grade B	EGD recorded 6/16/08 as Grade C

Protocol (b) (4) Subject	Source Document	CRF
1015	Withdrew consent reported as 5/14/08	Withdrew consent recorded as 11/24/08
1187	Diarrhea reported 8/26/08	Diarrhea not reported

b. Our inspection found that Subject 1148 participated in Protocol (b) (4), and that Subject 1195 participated in Protocol (b) (4); however, neither subject was listed on the Subject Identification Log for the relevant protocol.

c. Our inspection found that multiple source documents were missing from study records. Specifically:

Subject Protocol (b) (4)	Visit 1 Missing Documents	Visit 2 Missing Documents	Visit 3 Missing Documents	Visit 4 Missing Documents
1115	ECG printout			ECG printout
1120	ECG printout			
1166			All source documents missing	
Subject Protocol (b) (4)	**Visit 1 Missing Documents**	**Visit 2 Missing Documents**	**Visit 3 Missing Documents**	**Visit 4 Missing Documents**
1090			All source documents missing	
1144	All source documents missing except laboratory	All source documents missing except EGD	All source documents missing	All source documents missing except EGD and laboratory
1209	All source documents missing			

Failure to maintain adequate and accurate case histories, including the failure to maintain all source documents and the failure to ensure that data captured on CRFs is consistent with that contained in source documents, compromises the validity and integrity of data captured at your site.

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

As a clinical investigator, you are required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. In addition, Section 16.2 of the protocols referenced above states: "The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the site, the inventory at the site, the individual subject use record, and return of drug to a delegate of the sponsor." You failed to maintain adequate records of the disposition of the study drug, (b) (4), including dates, quantity, and use by subjects. Specifically:

a. Our inspection found that the Clinical Supplies Release & Receipt Form (CSRF) did not reconcile with the Site Investigational Product Inventory Log (SIPIL). For Protocol (b) (4), the CSRF recorded five (5) shipments totaling 24 kits to your site. However, the SIPIL indicates that 61 kits were received by your site. For

Protocol (b) (4), the CSRF recorded eight (8) shipments totaling 58 kits to your site. However, the SIPIL indicates that 128 kits were received by your site.

b. Our inspection found discrepancies between the Investigational Product Dispensing/Accountability Log (IPD/AL) and the SIPIL with respect to kits dispensed for the subjects listed below:

Subject # (protocol)	**Sponsor Kit Usage Form For Protocol (b) (4) only**	**Kits dispensed per IPD/AL**	**Kits dispensed per SIPIL**
1156 ((b) (4))		None	One
1185 (		One - #57279	None
1213 (		One - #57206	None
1163 (	One - #26936	One - #26936	None
1127 (	One - #21331	None	None

In particular, the Sponsor Kit Usage Form for Protocol (b) (4) notes that Kit # 21331 was dispensed to Subject 1127. However, neither the SIPIL nor the IPD/AL from your site reported that a kit was dispensed to Subject 1127. Furthermore, the IPD/AL from your site reports that Subject 1127 was not randomized.

c. Section 16.4 of the protocols referenced above states: "Each site must keep accurate records of the drug received at the site, and dispensed to and returned from the subjects."

Review of the IPD/ALs for both Protocol (b) (4) and Protocol (b) (4) shows that the date dispensed/returned and/or the initials of the staff member dispensing the kit were not recorded. For example:

Subject (Protocol (b) (4))	**Date Dispensed and/or Returned – Not recorded**	**Staff Initials – Not Recorded**
1110	x	x
1113	x	x
1120	x	x
1138	x	x
1148	x	x
1162	x	x
1163	x	x
1166	x	x

Subject (Protocol (b) (4))	Date Dispensed and/or Returned – Not recorded	Staff Initials – Not recorded
1015	x	x
1090	x	x
1107	x	x
1114	x	x
1133	x	x
1141	x	x
1151	x	x
1153	x	
1166	x	x
1167	x	x
1169	x	x
1175	x	x
1181	x	x
1190	x	x
1195	x	x
1201	x	x
1203	x	x
1213	x	x

Failure to maintain adequate and accurate records of drug received at your site and dispensed to or returned by subjects, raises concerns about the validity and integrity of the data at your site.

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 repeatedly or deliberately failed to comply with the cited regulations, which posed unnecessary risks to human subjects and jeopardized the integrity of data. 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.
Acting Director
Office 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

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
Office 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