DEPARTMENT OF HEALTH & HUMAN SERVICES

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

NOTICE OF OPPORTUNITY FOR HEARING (NOOH)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

Dear Dr. Mendolia:

The Center for Drug Evaluation and Research (the Center) of the U.S. Food and Drug Administration (FDA) has information indicating that you repeatedly or deliberately violated federal regulations in your capacity as an investigator in clinical trials with multiple investigational drugs. These violations provide the basis for withdrawal of your eligibility as a clinical investigator to receive investigational new drugs.

The Center's findings are based on information obtained during an FDA inspection, discussed below, of the following clinical studies for which you were the investigator of record:

1. Protocol (b) (4) : "(b) (4) " This study of the investigational drug (b) (4) was performed for (b) (4) .

2. Protocol (b) (4) : "(b) (4) " This study of the investigational drug (b) (4) was performed for (b) (4) .

FDA conducted an inspection between October 18, 2010, and November 1, 2010. After the inspection, and pursuant to Section 312.70(a) of Title 21 of the Code of Federal Regulations [21 CFR 312.70(a)], the Center informed you by letter entitled "Notice of Initiation of Disqualification Proceedings and Opportunity to Explain" (NIDPOE) dated November 22, 2011, of the specific matters complained of, and offered you an opportunity to respond in writing or at an informal conference. The NIDPOE also offered you the option of entering into a consent agreement with FDA, thereby terminating any administrative proceeding against you. In response to the NIDPOE, you requested an informal conference. On February 29, 2012, the

informal conference was held at FDA's facilities in Silver Spring, Maryland, with your participation by telephone. At the informal conference, you provided verbal explanations to the findings noted in the NIDPOE letter. You did not submit any supporting documentation before or after the informal conference.

After a review of all available information, the Center has concluded that the verbal explanations you provided at the informal conference are unacceptable because they fail to address adequately the violations set forth below.

Accordingly, you are being offered an opportunity for a regulatory hearing pursuant to 21 CFR parts 16 and 312, to determine whether you are entitled to receive investigational new drugs. You have the right to be advised and represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in 21 CFR part 16 and by FDA's guidelines on electronic media coverage of administrative proceedings, 21 CFR part 10, subpart C. Enclosed you will find copies of these regulations. A listing of the specific violations follows. These are matters that would be considered at the regulatory hearing if one is granted. 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 and a statement indicating that the patient is not eligible 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.

In response to Item 1a, you indicated at the informal conference that, with regard to the research coordinator, "there were never any issues … so I never had a reason not to trust what she had told me." You further indicated that if a test was positive, you were unaware of that and stated that you were "informed, perhaps, by her [the research coordinator], that the patient was eligible." You also stated that "there were lots of things that were either missing or falsified … that were disguised by [your] research coordinator," such that you, the CRO, and the sponsor were unaware of the problems.

Your response to Item 1a is inadequate because as clinical investigator, you are responsible for ensuring that ineligible subjects are not enrolled in studies, and you have not informed us of corrective actions taken to ensure that similar violations do not recur.

b. Section 9.3, Exclusion Criteria, in both 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 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) despite appearing to meet the exclusionary criterion of active alcohol abuse.

   In response to Item 1b (i), you indicated at the informal conference that the research coordinator failed to inform you that Subject 1184 had abnormal liver function tests. For Item 1b (ii), you indicated that the diagnosis of Barrett's esophagus was debatable histologically and not proven endoscopically. You indicated you would need to review the chart to debate this issue more accurately; however, you have not provided any documentation to refute Item 1b (ii) since the informal conference concluded. Regarding Item 1b (iii), you indicated that if you had been "informed correctly" by the research coordinator, the subject would not have been randomized.

Your response to Item 1b (i-iii) is inadequate because as a clinical investigator, you are responsible for ensuring that ineligible subjects are not enrolled in studies, and you have not informed us of corrective actions taken to ensure that similar violations do not recur.

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.

In response to Item 1c, you indicated at the informal conference that "perhaps the [study coordinator] did not transcribe them, or she [informed you] that they were done, and [you] assumed that they were done based on [the coordinator's] previous history" and your involvement in numerous studies with this research coordinator.

Your response to Item 1c is inadequate because as a clinical investigator, you are responsible for ensuring that required assessments are done, and you have not informed us of corrective actions taken to ensure that similar violations do not recur. You also provided no documentation to support a claim that the coordinator inaccurately transcribed information.

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 case report forms (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 6/17/08 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

*Esophagogastroduodenoscopy

In response to Item 2a, you indicated at the informal conference that the discrepancies between source documentation and CRFs represented errors made by your study coordinator. Your response is inadequate because as a clinical investigator, you are responsible for ensuring that information is accurately captured in source documents and CRFs, and you have not informed us of corrective actions taken to ensure that similar violations do not recur.

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.

In response to Item 2b, at the informal conference you stated, "Same response," referring to your response to Item 2a.

Your response is inadequate because as a clinical investigator, you are responsible for ensuring that the Subject Identification Log was accurate, and you have not informed us of corrective actions taken to ensure that similar violations do not recur.

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			

In response to Item 2c, you indicated at the informal conference that the research coordinator, the CRO, and the sponsor were responsible for the missing documentation.

Your response is inadequate because as a clinical investigator, you are responsible for maintaining source documents, and you have not informed us of corrective actions taken to ensure that similar violations do not recur.

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 Forms (CSRFs) 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 eleven (11) shipments totaling 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 fifteen (15) shipments totaling 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	
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

In response to Items 3a, b, and c, at the informal conference you stated, “It’s all the same response,” referring to your prior responses to Items 1 and 2.

Your response is inadequate because as a clinical investigator, you are responsible for maintaining adequate and accurate records of drug disposition, and you have not informed us of corrective actions taken to ensure that similar violations do not recur.

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.

Your request for a hearing must be made in writing within ten (10) business days after receipt of this letter, and should be directed to Capt. Sharon McCoy, Deputy Director, Division of Enforcement, Office of Enforcement and Import Operations, ORA, FDA, 10903 New Hampshire Avenue, WO32-4346, Silver Spring, MD 20993, telephone (301)796-8206, FAX (301) 847-8635. If no response to this letter is received by that time, you will be deemed to have waived any right to a regulatory hearing, and a decision in these matters will be made based on the facts available to FDA.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR 16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or his delegate determines that no genuine and substantial issue of fact has been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing.

If you wish to respond but do not desire a hearing, you should contact Capt. McCoy within the specified time period and send a written reply containing your response. The letter should state that you waive your right to a hearing, and that you want a decision on the matter to be based on your written response and other information available to FDA.

FDA's offer for you to enter into a consent agreement, attached to the NIDPOE letter dated November 22, 2011, remains available. Entering into a consent agreement would terminate the administrative procedures but would not preclude the possibility of a corollary judicial proceeding.

No final decision by FDA has been made at this time on your eligibility to continue to receive investigational new drugs. Moreover, there will be no prejudgment of this matter if you decline to enter into a consent agreement and decide instead either to request a regulatory hearing or to request that the decision be based on information currently available to FDA.

Please inform Capt. McCoy within ten (10) business days whether you wish to request a hearing or to have this matter resolved by consent agreement or information available to FDA.

Sincerely,

/Melinda Plaiser/
Melinda Plaisier
Acting Associate Commissioner
For Regulatory Affairs

Enclosures:
21 CFR part 10, subpart C
21 CFR part 16
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/

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