DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

MAY 19 1999

Arthur Riba, M.D.
18101 Oakwood Boulevard
Dearborn, Michigan 48123

Dear Dr. Riba:

Between February 5 and March 12, 1998, Ms. Nancy Mundo of the Food and Drug Administration (FDA) conducted an inspection of your clinical study (Protocol: [ ] entitled "A Randomized, Double-Blind Evaluation of the Efficacy and Safety of Two Dosing Regimens of Integrelin versus Placebo for Reducing Mortality and Myocardial (Re)Infarction in Patients with Unstable Angina or Non-Q Wave MI" (PURSUIT). The sponsor of this study is COR Therapeutics, and you are the investigator of record.

This inspection was conducted as part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research involving investigational products.

Based on evaluation of the information obtained, FDA's Center for Drug Evaluation and Research (Center) believes that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed) and that you submitted false information to FDA or the sponsor.

We have reviewed your March 19, 1998, response to the inspectional findings (Form FDA 483). In your letter you stated that your nurse was responsible for the misrepresentation of data and that you had no knowledge of this practice. We remind you that you are responsible for personally conducting or supervising the clinical investigations since you are the investigator of record. Therefore, we consider your explanation to be unacceptable.

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 supervise the clinical investigations as you committed to do when you signed the Form FDA 1572, in violation of 21 CFR 312.60 and 21 CFR 312.53(c)(1)(vi)(c).**

   Your lack of supervision caused the submission of false information to the sponsor in required reports for the study of investigational new drugs that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act, as demonstrated by the violative conduct described more fully below.

2. **You submitted false information to the sponsor and FDA, in violation of 21 CFR 312.70(a).**

a. The protocol required that the 30-Day Visit ECGs be obtained 28-42 days post randomization. The ECGs you submitted to the sponsor as "30-Day Visit ECGs" for eight (8) subjects were ***copies*** of ECGs obtained during the in-hospital phase of the protocol or at another time. The computer generated time and date ["Stamp Date"] on the in-hospital or other ECG for each subject was covered with a label; a new time and date were handwritten on each label ["Handwritten Date"]. The Handwritten Dates were reported on the CRFs to falsely indicate that the ECGs were done at a 30-Day post-randomization visit.

This table shows the subject number, the Date Enrolled, the Date Range within which a 30-Day ECG should have been done, the Handwritten Date, and the Stamp Date for each subject.

Subject #	Date Enrolled	Date Range 30-Day ECG Should Have Been Done	Handwritten Date on ECG label and/or CRF	Stamp Date
209609	4/27/96	5/25-6/8/96	7/3/96	3/29/96
247187	6/4/96	7/2-16/96	7/10/96	6/5/96
305422	8/10/96	9/7-21/96	10/10/96	8/11/96
317149	7/25/96	8/22-9/5/96	9/9/96	7/26/96
370642	10/16/96	11/13-29/96	11/21/96	10/19/96
383701	10/16/96	11/13-29/96	11/22/96	10/17/96
434474	11/27/96	12/24/96 - 1/7/97	1/2/97	# tops cut off; probably 11/26/96
442751	12/27/96	1/24-2/7/97	2/14/97	1/3/97

b. On 10/10/96, you reported on the 30 Day Visit CRF for Subject #305422 that this subject had an ECG on 10/10/96 and had no rehospitalizations. Hospital records show that this subject was hospitalized from 10/09/96 to 10/23/96 for cellulitis and septicemia related to the leg incision from bypass graft surgery.

3. You failed to conduct the clinical study in accordance with the approved protocol, in violation of 21 CFR 312.60 and 21 CFR 312.53(c)(1)(vi)(a).

a. For at least five (5) subjects, you "resubmitted" new "30-Day ECGs" [Replacement ECGs], when in fact these new ECGs were done anywhere between ***three months to one year after randomization.***

Subject #	Date Enrolled	Date Range 30-Day ECG Should Have Been Done	Replacement ECG Date
209609	4/27/96	5/25-6/8/96	4/17/97
247187	6/4/96	7/2-16/96	2/21/97
317149	7/25/96	8/22-9/5/96	4/17/97
383701	10/16/96	11/13-29/96	1/9/97
442751	12/27/96	1/24-2/7/97	4/15/97

b. Records obtained during an inspection of the study monitor[redacted] show that there are 46 subjects in addition to those listed in the table above (3a.) for whom you submitted "30-day ECGs," although the ECGs were taken anywhere from nine days prior to enrollment to 26 days post-randomization

c. The protocol states that "total creatinine kinase (CK) and MB isoenzymes will be done at the time of enrollment, and at 8 and 16 hours after enrollment." Fifteen (15) subjects who enrolled between 9/11/96 and 11/18/96 did not have cardiac enzymes ordered or performed.

d. The protocol specified the Primary Endpoint to be: "the composite of death from any cause or non-fatal myocardial (re)infarction during the first 30-Days after randomization." You were responsible for reviewing the 30-Day Form to ensure that information for each

subject, related to the Primary Efficacy Endpoint, was complete and correct; your review would have been documented by commenting on the significance of the data and/or signing the form. However, you have informed the agency that you did not review the 30-Day Form "since it was a simple follow up visit (or) no space was provided for the signature of the principal investigator on the 30-Day visit form."

4. **You failed to maintain adequate and accurate case histories, in violation of 21 CFR 312.62(b).**

a. The 30 Day Visit CRF for subject #397800 indicated that the subject was alive and that an ECG was performed on 12/6/96. However, this subject died on 11/8/96, one day after discharge from the hospital.

b. The ECG for Subject #267273 does not have a computer-generated date and time to show when the ECG was performed. Information on the ECG was covered by a label and a new time and date were handwritten on the label. There is no documentation in the subject's file to show who placed the label on the ECG, when the label was placed on the ECG, and why the document was modified.

5. **You failed to report adverse events, in violation of 21 CFR 312.64(b) and 21 CFR 312.53(c)(1)(vi)(e).**

a. Subject #135497 was enrolled on 3/4/96 and rehospitalized from 4/8/96 to 4/11/96 for neutropenia. This event was not reported to the sponsor.

b. Subject #196146 was enrolled on 3/11/96 and rehospitalized for atypical chest pain on 4/19/96. This rehospitalization was not reported to the sponsor.

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

On the basis of the above listed violations, the Center asserts that you have repeatedly or deliberately failed to comply with the cited regulations and that you submitted false information. The Center proposes that you be disqualified as a clinical investigator. You may reply in writing or at an informal conference in my office 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. 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) 594-0020 to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations (HFD-340)
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room #103
Rockville, Maryland 20855

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 all pertinent documents with you, and you may be accompanied by a representative of your choosing. 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 thirty (30) days of your request.

At any time during this administrative process, you may enter into a consent agreement with the Center 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 the Center.

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, 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.

Sincerely,

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research