DEPARTMENT OF HEALTH & HUMAN SERVICES

FEB 17 1999

Food and Drug Administration
Rockville MD 20857

CERTIFIED MAIL-RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

[ ]

NOTICE OF OPPORTUNITY FOR A HEARING

Dear Mr.[ ]

The Center for Drug Evaluation and Research (the Center) of the Food and Drug Administration (FDA) has information indicating that your client, Arthur Riba, M.D., repeatedly or deliberately violated federal regulations in his capacity as an investigator in a clinical study with the investigational new drug, Integrelin™ (eptifibatide). The Center also has information indicating that your client submitted false information to the sponsor in required reports. These violations provide the basis for withdrawal of Dr. Riba's eligibility as a clinical investigator to receive investigational new drugs.

The Center's findings are based on information obtained between February 5 and March 12, 1998, during FDA's inspection of the following clinical study for which Dr. Riba was the investigator of record:

> "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) [Protocol[ ]conducted for COR Therapeutics, Inc."

Pursuant to Section 312.70(a) of Title 21 of the Code of Federal Regulations (CFR), the Center informed Dr. Riba, by letter titled "Notice of Initiation of Disqualification Proceedings and Opportunity to Explain" (NIDPOE) dated May 19, 1999, of the specific matters complained of and offered him an opportunity to respond in writing or at an informal conference. The NIDPOE also offered Dr. Riba the option of entering into a consent agreement with the FDA, thereby terminating the administrative proceedings against him.

In response to the NIDPOE, you, as the attorney representing Dr. Riba, submitted a written explanation to the matters complained of in the NIDPOE. FDA has reviewed the explanation and accepts Dr. Riba's explanation for the following matters:

1. Item 3.c. on page 3 of the NIDPOE, regarding the use of the Troponin T assay in lieu of the CK/MB for 15 subjects.

2. Item 5.a. on page 4 of the NIDPOE, regarding the reporting of a rehospitalization of subject #135497 from 4/8/96 to 4/11/96.

The Center has concluded that Dr. Riba's written explanation for the remaining matters is unacceptable because it fails to adequately address the violations set forth below. You assert that "virtually all of the allegations in the Notice, however characterized, are traceable to the intentional misconduct of the clinical research nurse, [ ] R.N." However, this explanation is unacceptable because Dr. Riba, as the investigator of record, was responsible for personally conducting or supervising the clinical investigation.

Accordingly, Dr. Riba is being offered an opportunity for a regulatory hearing pursuant to 21 CFR Parts 16 and 312, to determine whether he is entitled to receive investigational new drugs. As you are aware, Dr. Riba has 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 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 will be considered at the regulatory hearing. Applicable provisions of the CFR are cited for each violation.

1. Dr. Riba failed to personally conduct or supervise the clinical investigation as he committed to do by signing the Form FDA 1572, in violation of 21 CFR 312.60 and 312.53(c)(1)(vi)(*c*). This lack of supervision allowed 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.

2. Dr. Riba submitted false information to the sponsor, in violation of 21 CFR 312.70(a). The protocol required that the 30-Day Visit ECGs be obtained 28-42 days post randomization. Dr. Riba submitted copies of ECGs obtained during the in-hospital phase of the protocol or at another time to the sponsor as "30-Day Visit ECGs" for at least eight (8) subjects. 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 Case Report Forms (CRFs) to falsely indicate that the ECGs were done at a 30-Day post-randomization visit.

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

A. For at least five (5) subjects, Dr. Riba "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 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. The protocol specified the Primary Efficacy Endpoint to be: "the composite of death from any cause or non-fatal myocardial (re)infarction during the first 30-Days after randomization." Dr. Riba violated the regulations by failing to ensure that the information recorded and forwarded to the sponsor on the "30-Day Form" regarding the subjects' status at approximately 30 days post-enrollment was complete and accurate. Dr. Riba asserts that there was no review of 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." This explanation lacks merit because this practice has an impact on the most important (and only protocol-specified) primary endpoint. The investigator of record must ensure correct and complete records regarding the Primary Efficacy Endpoint data. Dr. Riba committed to keeping complete and accurate records by signing the Form FDA 1572.

4. Dr. Riba failed to maintain adequate and accurate case histories for the following subjects, in violation of 21 CFR 312.62(b).

A. The CRF date on a 30-Day ECG for subject #397800 indicates that the subject was alive 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 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. Dr. Riba failed to report all adverse events, in violation of 21 CFR 312.64(b) and 312.53(c)(1)(vi)(*e*). 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.

Dr. Riba's request for a hearing must be made, in writing, within ten (10) business days after receipt of this letter and directed to Dr. James F. McCormack, Coordinator, Bioresearch Monitoring Program, Office of Enforcement, Division of Compliance Policy (HFC-230), 5600 Fishers Lane, Rockville, Maryland 20857, Telephone (301) 827-0425, FAX (301) 827-0482. If no response to this letter is received by that time, Dr. Riba will be deemed to have waived any right to a regulatory hearing, and a decision in this matter will be made without a hearing based on the facts available to FDA. No hearing will be held.

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 her delegate determines that no genuine and substantial issue of fact had 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 Dr. Riba wishes to respond but does not desire a hearing, he should contact Dr. McCormack within the time period specified above and send a written response containing his reply. The letter should state that Dr. Riba waives his right to a hearing and that he wants a decision on the matter to be based on his written response and other information available to FDA.

FDA's offer to enter into a consent agreement, attached to the NIDPOE dated May 19, 1999, 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 Dr. Riba's eligibility to continue to receive investigational new drugs. Moreover, there will be no prejudgment of this matter if Dr. Riba declines to enter into a consent agreement and decides instead either to request a regulatory hearing or to request that the decision be based on information currently available to FDA.

Please inform Dr. McCormack within ten (10) business days of whether Dr. Riba wishes to request a hearing or to have this matter resolved by consent agreement or information available to FDA.

Sincerely yours,

Dennis E. Baker
Associate Commissioner for
Regulatory Affairs

Enclosures:
21 CFR Part 10, Subpart C
21 CFR Part 16
21 CFR Part 312.70