DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Rockville MD 20857

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

APR 7 2000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

David P. Faxon, M.D.
Chief of Cardiology
University of Southern California
Ambulatory Health Center
1355 San Pablo Street, Suite 117
Los Angeles, California 90033

Dear Dr. Faxon:

Between October 5 and November 11, 1999, Mr. Richmond K. Yip of the Food and Drug Administration (FDA) conducted an inspection of your clinical study entitled: "[ ] versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post Acute Coronary Syndromes" The[ ]Trial) (Protocol: #[ ] of the investigational drug[,] performed for[ ] This inspection was conducted under FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the subjects have been protected.

Based on our evaluation of the information obtained by the agency, we believe that you have repeatedly or deliberately submitted false information as published under Title 21, Code of Federal Regulations (CFR), Part 312 (enclosure #3) and repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products.

We have reviewed your December 15, 1999, response to the inspectional findings (Form FDA 483), in which you stated that your study coordinator 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 and supervising the clinical investigations since you are the investigator of record. Therefore, we consider your explanation unacceptable in addressing the matters under complaint as outlined in this letter.

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.**

a. 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 violations described below.

b. Your lack of supervision allowed the study coordinator, who was not a licensed physician in California, to write medical orders that were not always co-signed by a licensed physician. For example, the study coordinator signed orders on physician order sheets for subjects[ ] #115-125,[ ]#105-415,[ ]#111-857, and[ ]#100-608.

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

a. Subject[ ](#100-752): The medical history sheet documented chest pain lasting 10-25 seconds since catheterization and PTCA in 12/97. Further down the same page of the medical history sheet was information that this pain lasted "20-25***." While "***" was alleged to represent "min" for minutes, it appears to be written over something else (which is not clearly visible). The chest pain duration of 10-25 seconds written on the upper portion of the same page indicated that "***" was falsified.

b. Subject[ ](#105-415): The patient medical history sheet, dated 3/31/98, documented chest pain lasting approximately 1 minute when walking for less than 1 block. There is a systems notation of chest pain in which the last episode lasted approximately "100 minutes" after walking more than 1 block, without the date of the last chest pain being recorded. It appears that two zeros have been added to "1" to make it "100 minutes". The subject's clinical history sheet dated 3/31/98, notes that chest pain occurs after walking less than 1 block which lasted approximately "91 minutes"; here, the number "9" appeared to have been added before the number "1" to make it "91".

c. Subject[ ](#115-125): The patient medical history sheet dated 3/27/98, listed a chest pain lasting "21 minutes" noted during a monitoring visit. However, during an earlier monitoring visit, a copy of the same page revealed that the same chest pain was documented as 1 minute. The number "2" appeared to be added before the number "1" to make it "21." Per the physician patient clinical history sheet, dated 3/28/98, the subject reported chest pain lasting for 1 minute after walking 1 block.

The protocol requires that each patient must have 20 minutes of chest pain for inclusion into the study. In each of the three instances noted above, we believe that the change in the duration of chest pain was made deliberately to qualify the subject for admission into the study.

3. You failed to conduct the clinical study in accordance with the approved protocol, in violation of 21 CFR 312.60

a. Subject[ ](#102-005): The case report form (CRF) documents that this subject qualified for enrollment on 2/11/98, 8 days prior to randomization, with a non-Q wave MI based on ECG changes and chest pain of 27 minutes duration. There was no source documentation to support chest pain duration as 27 minutes. The hospital physician notes on 2/11/98 and Emergency Department notes on 2/12/98 did not record any chest pain of 27 minutes, and the subject was admitted for shortness of breath and congestive heart failure.

1. According to the CRF, the subject was randomized on 2/19/98 (outside the enrollment window by 1 day). The study drug administration was delayed by 9 hours post randomization. In addition, the nursing flowsheet showed that the subject received Reopro, and was enrolled only 30.3 hours after completion of the Reopro infusion instead of protocol specified[ ]hours.

2. In addition to receiving Reopro (not reported in the CRF), this subject received prohibited concomitant medications: aspirin and 5 doses of Ticlid prior to randomization, and aspirin was administered after study drug administration.

3. Blood samples for this subject were not drawn for cardiac enzymes, 90-day ECG was not performed, and the subject was not randomized to the appropriate body weight class.

b. Subject[ ](#100-752): The subject's Record of Operation showed Reopro was administered on 3/24/98 at 09:16 hr, and the[ ]CRF shows that the first dose of study drug was administered on 3/25/98 at 2200. Thus, the requirement of a[ ]hour interval following Reopro infusion for randomization was not met.

c. Subject[ ](#107-180): This subject was found to be concurrently participating in the [ ]trial (enrolled 4/2/98) and a trial (enrolled 3/29/98). The[ ]trial requires administration of ASA (aspirin), an exclusionary criterion of the[ ]trial. The Medical Administration Record confirmed that ASA was administered daily, and other source documents indicated the subject continued to receive ASA during the study. Therefore, this subject should have been excluded from the[ ]trial.

d. Several subjects received prohibited concomitant medication during or within the window period of study drug administration. For example, medication records showed that subjects [ ]received three or more doses of Ticlid within hours prior to enrollment, and that subjects[ ]received three or more doses of Ticlid during study drug administration.

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

There were numerous discrepancies between case report forms and source documents. For example,

a. Subject[ ](#102-005): There were discrepancies in what was recorded for the subject's body weight (170 and 116 in the CRF vs. 199 to 220 in hospital charts); the CRF indicated an ECG was not performed at the 90-day visit, but there were two ECG tracings dated 5/20/90 at 06:43 and 13:46 on the 90-day visit; and the CRF reported the subject as a past smoker but notes made in subject's medical history, ER consultation dated 2/12/98, and nursing database dated 2/11/98 reported the subject was currently smoking 1 pack per day and had been for the past 35 years. Although the hospital records document that the subject received a stent on 2/17/98, the two-week summary in the CRF shows that the subject did NOT receive a stent.

b. Subject[ ](#105-218): The subject's medical history sheet in the CRF dated 4/1/98, the system review sheet, and a sample[ ]study order sheet listed chest pain every "2-3 weeks" with the most recent episode lasting 30-45 minutes and occurring when the subject presented in the clinic on 3/30/98. However, the subject's clinical history sheet dated 3/31/98 noted that the most recent chest pain was 8 weeks prior.

c. Subject[ ](#112-842): There were discrepancies between CRFs and source documents including height ("65" in the CRF vs. "60" in subject's clinical history sheet), date of signed informed consent (3/29/98 in the CRF vs. 3/25/98 in subject's clinical history sheet), and the first dose of study medication (1000 in CRF vs. 2100 in subject's clinical history sheet source document for 3/25/98).

d. Subject[ ](#115-125): The subject's CRF documents a MI on 1/98 whereas the physician's clinical history notes dated 1/13/98 indicated the subject did not have a MI. Lopressor was not reported in the CRF as a concomitant medication whereas the subject's medical history dated 3/27/98, nursing data base dated 3/27/98, clinical history dated 3/30/98 and 3/31/98, and discharge record dated 4/1/98 all document the subject received Lopressor.

e. Subject[ ](#101-878): The CRF listed the subject as a past smoker, but the medical history notes that the subject currently smoked 10 cigarettes per day and had for the past 10 years.

f. There was no source documentation to confirm the administration of study drug to subjects[ ](#115-125),[ ](#102-005),[ ](#110-517),[ ](#100-608),[ ](#105-415) and[ ](#105-218).

a. Subject[ ](#107-180): This subject is cited in 3.c above as enrolled in the study despite meeting exclusion criteria. In addition, the CRF for this subject did not record bleeding events or ischemic events as recorded in the following source documents. This subject experienced Bleed #1 (nose bleed) on 4/4/98 at 20:45, and Bleed #2 (puncture site), between randomization and the 2-week follow up visit, and a gingival bleed between the 2-week and 90-day visits, an ischemic experience lasting 65 minutes on 4/15/98 at 16:20, with elevation of Troponin and Q-wave changes and ST elevation in anterior leads in the ECG, as well as another episode of ischemic pain on 4/16/98 at 19:00 for 90 min with T-wave inversions in ECG.

b. Subject[ ](#102-005) experienced unstable angina that was not reported to the sponsor.

6. **You failed to administer the Spanish version of informed consent to subjects whose primary language was not English, in violation of 21 CFR 50.20.**

The Spanish version of informed consent was not provided to subjects[ ](#117-149), [ ](#105-534)[ ](#115-332),[ ](#115-125),[ ](#111-857),[ ](105-415), [ ](107-180) and[ ](#101-413) whose primary language was not English.

This letter is not intended to be an all-inclusive list of deficiencies for your clinical study of the investigational drug[ ] 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 repeatedly or deliberately submitted false information and failed to comply with the cited regulations and it 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-45)
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 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 (enclosure #4).

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 (enclosure #1) and 21 CFR 312.70 (enclosure #3). 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, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Enclosures:
#1 - 21 CFR 16
#2 – 21 CFR 50
#3 - 21 CFR 312.70
#4 - Proposed Agreement with Respect to Use of Investigational Products