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 - RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

Stephen D. Rossner, M.D.
97 Barnes Road
Wallingford, CT 06492

Dear Dr. Rossner:

Between March 4 and 10, 2005, Ms. Patricia Murphy and Ms. Michelle Noe, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigation:

Protocol[ ]entitled, "Effects of Blood Pressure Reduction on High Sensitivity C-Reactive Protein (hsCRP): A Multicenter, Randomized, Open-Label, 2-Arm Parallel Group to Evaluate the Efficacy of Moderate vs. Aggressive Antihypertensive Therapy with[ ]and[ ]to Reduce Blood Pressure and Plasma hsCRP levels in Patients with Stage 2 Hypertension." This study of the investigational drug[ ]was conducted by you for [ ]

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects participating in clinical research have been protected. We are aware that at the conclusion of the inspection, Ms. Murphy and Ms. Noe presented and discussed with you Form FDA 483.

We have evaluated the inspection report, the documents submitted with the report, other pertinent information obtained by the Agency, and your March 23, 2005 written response to the Form FDA 483, addressed to the District Office Director, Ms. Gail Costello. Based on our evaluation of this information, FDA's Center for Drug Evaluation and Research (the Center) believes that you have repeatedly or deliberately violated federal regulations governing the conduct of clinical studies involving investigational new drugs and the protection of human subjects under Title 21, Code of Federal Regulations (CFR), Parts

312 and Part 50 (copy enclosed), and that you submitted false information in a required report to the sponsor.

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 drugs as set forth under 21 CFR 312.70. A listing of the major violations follows. The applicable provisions of the CFR are cited for each violation.

1. You submitted false information to the sponsor in a required report [21 CFR 312.70(a)].

a. You falsified informed consent documents and case report forms (CRFs) to indicate that subjects had provided written informed consent when subjects had not provided such consent. In an affidavit completed by you during FDA's inspection (dated March 8, 2005), you admitted that subjects 001, 002, and 004 had not signed the informed consent documents and that you had signed these subjects' names on the informed consent documents some time after the subjects were enrolled in the study (i.e., that the subjects had not provided written informed consent). In addition, on the Visit 1/Day 0 Inclusion/Exclusion CRF that you submitted to the sponsor, you checked the box marked "yes" to indicate that subjects 001, 002, and 004 had provided written informed consent to participate in the study.

b. The protocol required that the subjects be randomized to receive either[ ] 160 mg daily or[ ]160/12.5 mg daily for 2 weeks, and after 2 weeks those receiving[ ]were to have their dose increased to 320 mg and those receiving[ ]were to have their dose increased to[ ]320/12.5 mg for a duration of 4 weeks. As described in greater detail below, you falsified CRFs to indicate that subjects were randomized to receive study drug in accordance with these protocol requirements, when in fact these subjects were administered study drug in a manner inconsistent with these requirements. In an affidavit completed by you during the inspection, you admitted that subjects did not always take the protocol-required dose and that, in some cases, you specifically instructed subjects to take half the protocol-required dose. The following CRFs were submitted to the sponsor:

i) The Visit 1/Day 0 CRF indicates that subject 001 was randomized to receive [ ]160/12.5 mg and the Visit 2/Week 2 and Visit 3/week 6 CRFs indicate that the subject's dose was increased to[ ]320/12.5 mg for the required 4 week period. However, source medical records indicate that the subject was dosed with[ ]80 mg and[ ]25 mg daily at study visit 1 and the dose of[ ]was increased to 160 mg at study visit 2.

ii) The Visit 1/Day 0 CRF indicates that subject 002 was randomized to receive [ ]160 mg and the Visit 2/Week 2 and Visit 3/week 6 CRFs indicate that

the subject's dose was increased to [ ]320 mg for the required 4 week period. However, source medical records indicate that the subject was dosed with [ ]80 mg and [ ]12.5 mg daily at study visit 1. There is no documentation in source records to indicate that this dose was changed at any time during the study.

iii) The Visit 1/Day 0 CRF indicates that subject [ ]was randomized to receive [ ]160 mg and the Visit 2/Week 2 and Visit 3/Week 6 CRFs indicate that the subject's dose was increased to 320 mg for the required 4 week period. However, source medical records indicate that the subject was dosed with [ ]80/12.5 mg daily at study visit 1. There is no documentation in source records to indicate that this dose was changed at any time during the study.

c. To be enrolled in the study, the protocol required that study subjects meet the protocol-specified criteria for hypertension--the mean of three (3) repeated seated measurements of systolic blood pressure of 160 to 185 mm Hg, inclusive, and/or diastolic blood pressure of 100 to 109 mm Hg, inclusive. As described in greater detail below, there were discrepancies between the blood pressure readings recorded in the CRFs and the source medical records at Visit 1 for subjects 001, 002, 003, and 004. In an affidavit completed by you during the inspection, you admitted that you recorded false blood pressure readings in the visit 1 CRFs so that subjects 001, 002, 003, and 004 would appear to meet the inclusion criterion for hypertension. The following CRFs were submitted to the sponsor:

i) In the Visit 1/Day 0 Inclusion/Exclusion CRF for subject 001, dated 6/8/04, you recorded blood pressure readings of 168/102 mm Hg, 166/100 mm Hg, and 166/102 mm Hg and you checked the box marked "yes" to indicate that the subject met the criteria for hypertension as defined by the protocol. However, source medical records for subject 001 for that same date recorded a blood pressure reading of 150/80 mm Hg.

ii) In the Visit 1/Day 0 Inclusion/Exclusion CRF for subject 002, dated 6/9/04, you recorded blood pressure readings of 174/100 mm Hg, 170/100 mm Hg, and 170/100 mm Hg and you checked the box marked "yes" to indicate that the subject met the criteria for hypertension as defined by the protocol. However, source medical records for subject 002 for that same date recorded a blood pressure reading of 140/80 mm Hg.

iii) In the Visit 1/Day 0 Inclusion/Exclusion CRF for subject 003, dated 6/9/04, you recorded blood pressure readings of 164/102 mm Hg, 160/102 mm Hg, and 164/100 mm Hg and you checked the box marked "yes" to indicate that the subject met the criteria for hypertension as defined by the protocol. However, source medical records for subject 003 for that same date recorded a blood pressure reading of 142/80 mm Hg.

iv) In the Visit 1/Day 0 Inclusion/Exclusion CRF for subject 004, dated 6/10/04,

you recorded blood pressure readings of 168/98 mm Hg, 164/100 mm Hg, and 164/100 mm Hg and you checked the box marked "yes" to indicate that the subject met the criteria for hypertension as defined by the protocol. However, source medical records for subject 004 for that same date recorded a blood pressure reading of 118/80 mm Hg.

d. The protocol required that subjects who were on pharmacologic antihypertensive therapy with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, aldosterone blockers, or thiazide diuretics (hereafter "prohibited antihypertensive therapy") within 3 months prior to visit 1 be excluded from the study. As described in greater detail below, in CRFs for subjects 001, 003, and 004 you indicated that the subjects had not taken prohibited antihypertensive therapy during the 3 months prior to enrollment in the study when source documents indicated that subjects had been taking prohibited antihypertensive therapy. In an affidavit completed by you during the inspection, you admitted that there were discrepancies between CRFs and source medical records concerning subjects' past medical histories and that certain subjects did not meet the inclusion criteria because they were controlled on antihypertensive medication prior to enrollment. The following CRFs were submitted to the sponsor:

i) In the Visit 1/Day 0 Inclusion/Exclusion CRF for subject 001, dated 6/8/04, you checked the box marked "no" to indicate that the subject had not received prohibited antihypertensive therapy in the 3 months prior to that date. However, source records for subject 001 dated 4/26/04 indicate that the subject was on Benicar (olmesartan medoxomil), an angiotensin receptor blocker, and hydrochlorothiazide, a thiazide diuretic. Records dated 5/4/04 indicate that Benicar was discontinued on that date, but this occurred well within the 3 month window.

ii) In the Visit 1/Day 0 Inclusion/Exclusion CRF for subject 003, dated 6/9/04, you checked the box marked "no" to indicate that the subject had not received prohibited antihypertensive therapy in the 3 months prior to that date. However, source records for subject 003 dated 4/28/04 indicate that the subject was prescribed Diovan, an angiotensin receptor blocker, on that date.

iii) In the Visit 1/Day 0 Inclusion/Exclusion CRF for subject 004, dated 6/10/04, you checked the box marked "no" to indicate that the subject had not received prohibited antihypertensive therapy in the 3 months prior to that date. However, source records for subject 004 dated 4/30/04 indicate that the subject was prescribed Diovan, an angiotensin receptor blocker, on that date.

e. The protocol required that potential subjects be excluded from the study if certain laboratory parameters were outside the ranges specified in the protocol in the 3

months prior to visit enrollment, including serum creatinine >2.0mg/dL and any serum AST or ALT elevation that is twice the upper limit of normal. As

described in greater detail below, our investigation found that you did not obtain all of the required laboratory values for subjects enrolled in the study. In an affidavit completed by you during the inspection, you admitted that you recorded false information on the case report forms for subjects 001, 002, 003, and 004 to indicate that the certain laboratory results met eligibility criteria when the required laboratory evaluations had not been done. The following CRFs were submitted to the sponsor:

i) In the Visit1/Day 0 Inclusion/Exclusion CRF for subject 001, dated 6/8/04, you checked the box marked "no" to indicate that the subject's laboratory values for serum AST and ALT were not outside the specified ranges. However, a laboratory report for subject 001 dated 4/15/04 indicates that serum AST and ALT testing was not done. There is no other documentation of laboratory testing having been done during the 3 month period prior to the subject's enrollment.

ii) In the Visit1/Day 0 Inclusion/Exclusion CRF for subject 002, dated 6/9/04, you checked the boxes marked "no" to indicate that the subject's laboratory values for serum creatinine and serum AST and ALT were not outside the specified ranges. However, a laboratory report for subject 002 dated 6/9/04 indicates that serum creatinine and serum AST and ALT testing were not done. There is no other documentation of laboratory testing having been done during the 3 month period prior to the subject's enrollment.

iii) In the Visit1/Day 0 Inclusion/Exclusion CRF for subject 003, dated 6/9/04, you checked the box marked "no" to indicate that the subject's laboratory values for serum AST and ALT were not outside the specified ranges. However, a laboratory report for subject 003 dated 6/9/04 indicates that serum AST and ALT testing was not done. There is no other documentation of laboratory testing having been done during the 3 month period prior to the subject's enrollment.

iv) In the Visit1/Day 0 Inclusion/Exclusion CRF for subject 004, dated 6/10/04, you checked the box marked "no" to indicate that the subject's laboratory values for serum AST and ALT were not outside the specified ranges. However, a laboratory report for subject 004 dated 6/10/04 indicates that serum AST and ALT testing was not done. There is no other documentation of laboratory testing having been done during the 3 month period prior to the subject's enrollment.

2. **You failed to obtain the legally effective informed consent of subjects participating in the study [21 CFR 50.20, 50.27, and 312.60].**

   An investigator is responsible for obtaining the informed consent of each human subject to whom study drug is administered in accordance with the requirements of 21 CFR Part 50 (see 21 CFR 312.60). In particular, informed consent is required to be documented by use of a written consent formed approved by an IRB[1] and signed and dated by the subject or the subject's legally authorized representative at the time of consent (21 CFR 50.27(a)). Our investigation found that, for subjects 001, 002, and 004, you did not document their informed consent by the use of a written consent form signed and dated by the subjects. Furthermore, in an affidavit completed by you during the inspection, you stated that you "verbally told the subjects about the study," and admitted that you signed these subjects' names on the informed consent documents some time after the subjects had been enrolled in the study. Therefore, you did not obtain the legally effective informed consent of subjects 001, 002, and 004.

3. **You failed to ensure the studies were conducted according to the investigational plan [21 CFR 312.60].**

   a. The protocol required that the subjects be randomized to receive either[ ] 160 mg daily or[ ]160/12.5 mg daily for 2 weeks, and after 2 weeks those receiving[ ]were to have their dose increased to 320 mg and those receiving[ ]were to have their dose increased to[ ]320/12.5 mg for a duration of 4 weeks. Subjects 001, 002, and 003 were not dosed in accordance with the protocol. (See violations #1.b.i-iii above.)

   b. The protocol required that subjects meet the protocol-specified criteria for hypertension to be enrolled in the study--the mean of three (3) repeated seated measurements of systolic blood pressure of 160 to 185 mm Hg, inclusive, and/or diastolic blood pressure of 100 to 109 mm Hg, inclusive. Subjects 001, 002, 003, and 004 did not meet the criteria for hypertension specified in the protocol, but were nonetheless enrolled in the study. (See violations #1.c.i-iv above.)

   c. The protocol excluded subjects who were on pharmacologic antihypertensive therapy with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, aldosterone blockers, or thiazide diuretics within 3 months prior to visit 1. Subjects 001, 003, and 004 were taking prohibited antihypertensive therapies within the 3 month period prior to visit 1, but were nonetheless enrolled in the study. (See violations #1.d.i-iii above.)

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1 Written consent is required unless an IRB determines there is a basis to waive the requirement for written consent. To waive the requirement an IRB must determine that the study presents no more than minimal risk or the study meets the requirements for an exception from informed consent for emergency research 21 CFR 56.109(c)Neither exception applies to Protocol[ ]

d. The protocol excluded subjects if certain laboratory parameters were outside the protocol-specified ranges in the 3 months prior to visit 1, including serum creatinine >2.0mg/dL and any serum AST or ALT elevation that is twice the upper limit of normal. In an affidavit completed by you during the inspection, you acknowledged that you did not obtain results of certain required laboratory testing (serum creatinine and/or serum AST and ALT) at study visit 1, or within the 3 months prior to study visit 1, for subjects 001, 002, 003, and 004. These subjects were nonetheless enrolled in the study. (See violations #1.e.i-iv above.)

4. **You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each subject [21 CFR 312.62(b)].**

a. The protocol specified that all concomitant medications must be recorded on the Concomitant Medication/Significant Non-Drug Therapies CRF. Our investigation found that subjects 001, 002, 003, and 004 were taking concomitant medications during the study, but these medications were not recorded in the appropriate CRFs. In an affidavit completed by you during the inspection, you acknowledged that information on concomitant medications recorded in the CRFs did not always match information recorded in source medical records. For example:

i) Source medical records indicate that subject 001 was taking Lopressor 25 mg daily during the study, but this information was not recorded in the CRF.

ii) Source medical records indicate that subject 002 was taking Lipitor during the study, but this information was not recorded in the CRF.

iii) Source medical records indicate that subject 003 was taking Lipitor, and aspirin during the study, but this information was not recorded in the CRF.

iv) Source medical records indicate that subject 004 was taking Hytrin, Norvasc, hydrochlorothiazide, aspirin, and lovastatin during the study, but this information was not recorded in the CRF.

b. The protocol required that adverse events be recorded in the Adverse Event CRF. The protocol defines "adverse event" as any undesirable sign, symptom or medical condition occurring after starting study drug. According to source medical record for subject 001, the subject experienced dizziness while on study medication, but this adverse event was not recorded in the Adverse Event CRF.

c. Our investigation found that the initials of four subjects enrolled in the study were inaccurate. You recorded the following initials in study documents (e.g., case report forms and informed consent documents) for the subjects who were enrolled in the study: 001[ ] 002[ ] 003[ ] and 004[ ] During the inspection, you admitted that you enrolled subjects under different initials and that

the correct initials were those contained in the medical records. The initials recorded in the medical records were as follows: 001[ ]002[ ]003 [ ]and 004[ ]

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, the Center asserts that you have repeatedly or deliberately failed to comply with the cited regulations and submitted false information to the sponsor in a required report. Your actions have exposed human subjects to unnecessary risks and jeopardized the integrity of data. The Center 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) 594-0020 to arrange a conference time or to indicate your intent to respond in writing.

Should you choose 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:

Joseph Salewski
Director (Acting)
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
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 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 the FDA.

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 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.

Sincerely yours,

{See appended electronic signature page}

Joseph Salewski
Director (Acting)
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosures:
1. 21 CFR 16
2. 21 CFR 312.70
3. Consent Agreement

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph Salewski
5/10/2006 12:46:00 PM