DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

M3606(1)

CBER–00-022

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

WARNING LETTER

APR 28 2000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Jeffrey M. Isner, M.D
Chief, Vascular Medicine
St. Elizabeth's Medical Center
736 Cambridge Street
Boston, Massachusetts 02135

Dear Dr. Isner:

During an inspection ending on March 22, 2000, Ms. Paraluman Leonin, an investigator with the Food and Drug Administration (FDA), met with you to review your conduct of several clinical studies using Vascular Endothelial Growth Factor Plasmid (VEGF- [redacted] and VEGF-2) in human subjects with cardiac or peripheral artery disease. Dr. Dwaine Rieves and Mr. Jose Javier Tavarez from FDA's Center for Biologics Evaluation and Research (CBER) participated in the inspection of your clinical site. Vascular Genetics Incorporated, St. Elizabeth's Medical Center, and Dr. Jeffrey Isner sponsor the clinical studies. The inspection was conducted under FDA's Bioresearch Monitoring Program that includes inspections designed to monitor the conduct of clinical research involving investigational drugs.

Based on information obtained during the inspection, we have determined that you have violated regulations governing the proper conduct of clinical studies involving investigational new drugs and the protection of human subjects, as published in Title 21, Code of Federal Regulations, Parts 312 [21 CFR 312] and 50 [21 CFR 50], respectively. The outcome of the FDA audit/inspection raised concerns about the quality of your clinical research. This letter addresses your duties as principal investigator. Your activities as a sponsor of research with an investigational vector will be discussed in a separate letter.

In accordance with 21 CFR 312.60 and Part 50, an investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan (protocol), and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. Our investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of investigational new drugs for the reasons listed below. The applicable provisions of the CFR are cited for each violation.

1. **Failure to ensure that the investigation is conducted according to the investigational plan (protocol) and failure to protect the welfare of subjects under the investigator's care. [21 CFR 312.60]**

   a. Subject ——— was enrolled into study VEGF2-CAD-CL-001 (cardiac arterial disease study); however, the subject met the protocol exclusion criteria. The protocol excludes those subjects with any evidence of cancer. This patient had a prominent lung mass detected on at least two chest radiographs prior to administration of the study drug. Following enrollment and treatment in the study, this subject was ultimately diagnosed by the local private physician as having nonresectable cancer. The following chronology indicates a serious lack of study oversight and supervision of personnel involved in this study.

Subject ——— had a history of smoking and had been noted as having a < 1 cm left upper lobe lung nodule by his private physician. Reports of chest CT scans (computerized tomography scan) performed by the patient's private physician on January 14, 1999 and July 8, 1999, were submitted to you. The January, 1999 scan report indicates the presence of a < 1 cm lung nodule. The July, 1999 scan report does not identify this nodule. The nurse/study coordinator noted that Dr. Douglas Losordo (a sub-investigator) saw the CT scan report. However, there is no documentation in the subject's records to indicate that the outside chest CT films were reviewed by clinicians at St. Elizabeth's Medical Center. The subject underwent a screening chest radiograph at St. Elizabeth's on August 26, 1999, requested by Dr. Losordo, and interpreted on August 26, 1999 by Dr. ———. Dr. ——noted in her radiograph report:

" There is an ill-defined density in the left upper lobe. The margins are subtle but measure roughly 2 by 2 cm. The patient should have a CT scan of the chest unless there is an outside old chest x-ray showing a similar unchanged finding. Dr. Losordo's nurse has been told of the need for further follow-up on this patient as Dr. Losordo is in a procedure."

There is no documentation that the August 26, 1999 chest radiograph finding was evaluated by the principal investigator or sub-investigators prior to administration of the study drug, nor evidence of a 2 cm lung lesion prior to August 26, 1999. These findings document that the subject had a marked increase in size of the lung nodule prior to study enrollment, compared to the CT Scan evaluations from January and July, 1999.

The subject's Exclusion Criteria Form was completed on September 17, 1999. In response to the question, "does the patient have any evidence (clinical, laboratory or imaging) of cancer?" the "no" box was checked.

The subject was admitted to St. Elizabeth's Medical Center on September 20, 1999, and received an intracardiac injection of the VEGF-2 plasmid on September 21, 1999. During the FDA Inspection, Dr. Dwaine Rieves examined a chest radiograph from September 20, 1999. The radiograph shows a prominent left upper lobe lung lesion. The subject's clinical records did not contain the radiologist's report of this radiograph. Chest radiographs were also obtained on September 22, 1999 and September 24, 1999, following administration of the study drug. The chest radiograph report of September 22

describes a 2.8 cm left upper lobe lung mass, while the other report describes the mass as unchanged since August 26, 1999. The subject underwent a chest CT scan on September 24, 1999 and the radiologist reported "There is a 2.5 cm sized mass in the left upper lobe..."

The September 27, 1999 discharge summary (dictated by Dr. ————) reports that the subject was referred for consideration of "gene therapy surgery" and accepted into the "gene therapy program" and mentions neither a lung lesion nor the need for evaluation of a lung lesion. The summary states the subject was discharged to home with follow-up according to the Gene Therapy team of Dr. Jeffrey Isner.
No documentation of communication to the subject or private physician of the detection of a lung mass was present in the subject's clinical records, hospital chart, or case report form.

The subject's clinical records contain a discharge summary from a hospital in his home state that indicates the subject was hospitalized from November 26-30, 1999 because of chest pain. A left lung mass was detected and it was noted the mass needed evaluation.

The subject was readmitted to St. Elizabeth's on December 10, 1999 for protocol-specified follow-up coronary arteriography. A chest radiograph from December 10, 1999 reports, "There is a 5 cm sized mass in the left upper lobe posteriorly. In comparison with the previous chest films on September 24, 1999, it has become larger in size. Dr. Douglas Losordo has been called with the findings." On December 10, 1999, Dr. Losordo sent a letter to one of the subject's private physicians and stated that the subject "has had a significant reduction of his symptoms since gene therapy." Dr. Losordo provides no information regarding the 5 cm left lung mass.

The Adverse Events Log Form (undated) for subject ———— for the period of "treatment phase through post-treatment phase," records that the subject has a "left lobe lung mass increased in size." The "medical intensity" of the adverse event was initially marked as "severe," but was changed to "mild" by an individual with the initials "LMG." The rapid growth of this mass while on study raises substantial concerns that it is a malignancy and that it has progressed and is nonresectable. A reasonable possibility exists that circulating VEGF-2 contributed to the tumor growth; the lack of a VEGF-2 assay limits the ability to assess this possibility. Additionally, the form confirms that no action was taken following the report of increase in size of the lung mass. This adverse event was not reported in a timely manner to the Institutional Review Board.

The findings described above concerning subject ———— indicate the following:

(i) Subject ———— was enrolled in violation of protocol eligibility criteria, as there was evidence suggesting the presence of lung cancer. Source documents show the first identification of a lung mass in this subject was the screening chest radiograph of August 26, 1999. Despite the evidence of possible cancer, the subject was enrolled. The subject's history of no nodule being evident in July 1999, and a prominent mass in August and September 1999 radiographs, indicates that the lung lesion should have been evaluated prior to administration of the study drug. During the inspection, you confirmed that you had not

examined the subject's chest radiographs. No documentation indicates that you reviewed the subject's Inclusion and Exclusion Criteria Form or screening assessments to confirm the subject's eligibility for study participation.

(ii) The sub-investigator appears to have inadequately evaluated the subject during conduct of the study, including the screening assessments.

(iii) Your site appears to have failed to provide adequate medical care for this subject. Review of the Adverse Events Log Form for subject ——— confirms that no actions were taken following the reported increase in size of the lung mass. Review of the clinical records, hospital chart and case report form indicate no documentation of communication to the subject or private physician of the detection of a lung mass.

b. Subject —— was enrolled into study VEGF2-PAD-CL-005 (peripheral arterial disease study), but did not meet protocol inclusion criteria. The subject had a resting ankle-brachial index (ABI) in the affected limb of more than 1.0, while the protocol requires an ABI in the affected limb of less than 0.6.

The enrollment of ineligible subjects can be a serious protocol deviation. Treatment of subjects outside the approved protocol may have exposed them to an unreasonable and significant risk of illness or injury, as well as affecting the final results of the study.

c. Protocol exclusion criteria appear not to be assessed for two subjects (—— and ——) enrolled into study VEGF2-PAD-CL-007. Review of a source document revealed that none of the items under exclusion criteria were "check marked" to indicate that the subject did not meet the exclusion criteria. Subjects were to be excluded if they were lactating, pregnant and/or had cancer.

d. The absolute ankle and toe pressures, and the ABI and GTI assessments were not done for subjects —— and —— during the post-treatment phase (week 10 and 12) and treatment phase, respectively. (VEGF2-PAD-CL-005 study)

e. Many subjects did not have physical examinations or complete physical examinations during the treatment phase and/or post-treatment follow-up (VEGF2-PAD-CL-005 study). The following is a table for physical examinations that were either not done (ND) or incomplete (I):

Subject No.	Treatment Phase	Post-treatment Phase (weeks after treatment)							
		1	2	3	4	5	6	10	12
			ND	ND	ND		ND		I
	ND	ND					I		I
		ND	ND	ND					
		I		I					
	I	I						I	
	I	ND				I			

f. The edema score and Rutherford clinical severity score assessments were not done for subject —— during the screening/baseline phase of study VEGF2-PAD-CL-005.

g. The weight and height were not determined for subjects —— and —— during the screening/baseline phase of VEGF2-PAD-CL-005 study.

h. The injection site evaluation was not done for subject —— during the post-treatment phase (week 1) of VEGF2-PAD-CL-005 study.

i. The GTI and osteomyelitis assessments were not performed during screening phase for subjects —— and —— enrolled into study VEGF2-PAD-CL-001.

j. Vital sign assessments, including temperature, blood pressure, pulse and respiratory rate were not done for several subjects enrolled into study VEGF2-PAD-CL-005. The following is a table for vital sign assessments that were either not done (ND) or incomplete (I):

Subject No.	Screening/ Baseline Phase	Treatment Phase	Post-treatment Phase (weeks after treatment)		
			1	10	12
			ND	ND	ND
		ND	I		
	ND	ND			
	ND				
	ND				

k. Several subjects enrolled into study VEGF2-PAD-CL-005 did not have complete laboratory tests performed as per protocol. These laboratory results are an important part of the overall safety assessment of the study drug. The following is a table for hematology, chemistry, urinalysis, or hemoccult stool tests that were not done (ND) or were only partially done (P):

Subject No.	Screening/Baseline Phase			
	Chemistry	Hematology	Hemoccult Stool	Urinalysis
	P	P	ND	ND
	Treatment Phase			
	ND	ND	ND	ND
	Post-treatment Phase (week 1)			
	ND	ND	ND	ND

The principal investigator is to ensure that all tests and evaluations are conducted as indicated in the protocol. Missing tests, tests performed outside of protocol-specified timeframes, missed follow-up visits, and other missing clinical procedures can adversely affect patient safety, as well as safety and efficacy analyses of data.

l. According to the protocol, blood samples for determination of VEGF-2 plasma levels were to be drawn several times during the study. Blood samples were not collected for several subjects. For example:

i. Subject —— during the post-treatment phase week 1 of study VEGF2-PAD-CL-005.

ii. Subject —— during the treatment period day 1 and post-treatment period (24 hours after dosing) of study VEGF2-CAD-CL-005.

iii. Subject —— .during post-treatment period week 2 of study VEGF2-CAD-CL-005.

iv. There is no documentation on the source documents to indicate that blood samples for determination of plasma VEGF-2 levels were collected for subjects —— and —— .(study VEGF2-CAD-CL-005).

m. Blood samples for determination of serum VEGF-2 antibodies were not collected for subject —— during the treatment period day 1 and post-treatment period week 12 of study VEGF2-CAD-CL-005.

2. Failure to obtain informed consent in accordance with the provisions of 21 CFR Parts 50 and 56. [21 CFR 312.60]

The consent form requires the signature of a witness and the principal investigator or representative who is present during the entire consent interview. Subjects —— and —— signed the consent form on May 11, 1999; however, the witness signed the consent form on August 2, 1999, three months later. (Protocol VEGF2-PAD-CL-005)

3. Failure to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation. [21 CFR 312.62(b)]

Protocol VEGF2-PAD-CL-005

a. A source document dated July 27, 1999, signed by Dr. Isner, reports that the great-toe index was not measurable for subject —— . A document from St. Elizabeth's Vascular Lab dated 3/1/99 reports that the GTI was not measured, but did not give a reason.

b. The Diary Data Extraction Form for the post–treatment phase (week 2 and 3) for subject —— was not completed to document whether any adverse events/medications were recorded in the subject's diary. Conceivably, adverse events/medications were not transcribed to the case report form.

c. Failure to document the causal basis for a subject's termination. The Termination Record for subject — indicates that the subject was prematurely discontinued from study VEGF2-PAD-CL-005 and does not document the reasons for early termination. The Termination Record only documents that the subject was enrolled in the VEGF2-PAD-CL-007 study.

d. Utilization of correction fluid/white-out for correction of data entries on several source documents (e.g., PVR Flowsheet for subject —).

e. Data entries on several source documents or case report forms were done using a pencil. For example, data entries made on 8/30/99 and 3/9/2000 regarding neurological examination of the affected limb for subject —.

4. Failure to notify the Institutional Review Board (IRB) of all unanticipated problems involving risk to human subjects or others. [21 CFR 312.66]

a. You submitted an annual report to the IRB for the period September 3, 1998 through January 15, 1999. Concerning subject —, enrolled in study VEGF-—, the annual report to the IRB states "one patient required a two month hospital stay secondary to her inability to wean off the ventilator." However, the subject's death which had occurred on October 23, 1998, three months prior to the IRB report, was not mentioned in the report. You failed to submit an accurate and complete annual report to the IRB.

The inspection revealed that you performed and reported the cardiac portion of an autopsy for subject — and were well aware of the death.

b. Subject —, enrolled in study VEGF2-CAD-CL-001, had an adverse event that was not reported to the IRB in a prompt and timely manner. The subject had a chest X-ray on December 10, 1999, showing evidence of substantial lung mass growth; however, no adverse event was submitted to the IRB until February 17, 2000.

It is the investigator's responsibility to report all adverse experiences of a serious or unexpected nature to the responsible IRB and the sponsor. These adverse experiences should also be reported on the case report form.

Subject — received a direct cardiac injection of the VEGF- — product on June 9, 1998, suffered cardiac arrest in the perioperative period, leading to multi-system organ failure, prolonged hospital stay, and died October 23, 1998. The chief pathologist harvested the heart and turned it over to you. There was no histopathological heart examination by a pathologist. The chief pathologist confirmed to FDA that you performed all anatomic and histopathologic examination of the heart. He and Mr. Jeffrey Allard (Medical Administration, Department of Medicine) confirmed that you had no hospital privileges for the performance of autopsies. Your curriculum vitae does not denote that you are board certified in pathology

Deviations in these studies appear to be the result of a serious lack of knowledge of your responsibilities as principal investigator including supervision of personnel. Staff who were delegated the authority to perform certain functions were not adequately trained and monitored. Although authority may be delegated, the principal investigator is ultimately responsible for study conduct. Please provide us with assurance that all study personnel, including the study coordinator and sub-investigators, are trained in good clinical practice.

You deviated from an authorized study plan, investigator statement, or other conditions imposed on the study by the sponsor, IRB, or FDA. Your signature on Form FDA 1572, Statement of Investigator, indicates your agreement to comply with all requirements regarding the obligations of clinical investigators conducting human clinical trials and all other pertinent requirements in 21 CFR Part 312.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of the investigational drugs VEGF-[redacted] and VEGF-2. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations. We request that you inform us, in writing, within fifteen (15) business days after receipt of this letter, of the steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. If corrective action cannot be completed within 15 business days, state the reason for the delay and the time within which the corrections will be completed.

Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs or termination of an investigational new drug application (IND).

Please send your written response to:

Jose Javier Tavarez, M.S.
FDA/Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Bioresearch Monitoring Branch (HFM-650)
1401 Rockville Pike
Rockville, Maryland 20852-1448

Please send a copy of your response to FDA's New England District Office, Director, Compliance Branch, One Montvale Ave., 4th Floor, Stoneham, Massachusetts 02180. If you have questions concerning this matter, please contact Mr. Tavarez at (Tel.) 301-827-6221.

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

cc: Michael Collins, M.D.
President
St. Elizabeth's Medical Center
736 Cambridge Street
Boston, Massachusetts 02135

Alan Ashare, M.D., Chairman
Research – Human Subjects Committee
St. Elizabeth's Medical Center
736 Cambridge Street
Boston, Massachusetts 02135

Ms. Lynda Sutton
Senior Vice President, Regulatory Affairs
Vascular Genetics Incorporated
200 Westpark Corporate Center
4364 South Alston Avenue
Durham, North Carolina 27713