

## 1) SCIENTIFIC ABSTRACT OF THE CLINICAL PROTOCOL

The plasmid pVGI.1(VEGF2) contains the deoxyribonucleic acid sequence for vascular endothelial growth factor 2 (VEGF-2), a member of a class of natural growth factors that promote angiogenesis. The Sponsor has studied VEGF-2 gene transfer, delivered either via an epicardial approach via a mini-thoracotomy during surgery or via an endocardial approach using a percutaneous transvalvular cardiac catheter. These studies were conducted in patients with refractory, stable Canadian Cardiovascular Society class III or IV angina who were not considered to be suitable candidates for conventional revascularization procedures ("No option"). These preliminary studies have indicated that intramyocardial delivery of pVGI.1 (VEGF2) at doses up to and including 2 mg are safe and to be associated with improvements in exercise tolerance and in angina class. The present study will evaluate three doses of pVGI.1 (VEGF2) (2, 200 or 2000 µg) vs. placebo in a double-blind fashion in the same class of patient.

This study will enroll "no option" patients who are considered to have refractory, stable Canadian Cardiovascular Society class III or IV angina who are not suitable candidates for conventional revascularization procedures.

The primary efficacy objective of this study is to compare the effect of three intramyocardial doses of pVGI.1 (VEGF2) (2, 200 or 2000 µg) vs. placebo treatment when given by using an injection cardiac catheter on the change from baseline in exercise duration at 3 months after treatment.

The secondary objectives of this study are to compare the effect of the three doses of pVGI.1(VEGF2) versus placebo treatment on the change from baseline in angina class, NTG use, myocardial perfusion by SPECT, and patient functional status Seattle Angina Questionnaire (SAQ) at 3 months after treatment. In addition the changes in exercise duration, angina class, and patient functional status will be evaluated at intervals over the 1-year Follow-up Period.

The safety of the various doses of pVGI.1 (VEGF2) will be evaluated on an ongoing basis over the duration of this study by the sponsor designated medical monitor and on a periodic basis by a Data and Safety monitoring board (DSMB). Periodic interim safety evaluation of pVGI.1 (VEGF2) are scheduled to occur after 50, 100 and 250 patients have been randomized, treated and have completed their 2 week (14 day) post injection safety evaluations.

The study will consist of an optional Run-in Period (4 weeks), a Baseline Period (up to 4 weeks), a Treatment Period (Days 1 through 3), a Post-treatment Period (Out to Month 12) during which the study objectives will be evaluated for protocol defined outcomes followed by a Long-term (15 year) Post-Treatment Follow-up phase. During the Run-in Period, anti-anginal medication may be optimized on an individual patient basis. The Run-in Period may be waived if documentation indicates that a potential patient is currently taking maximally tolerated doses of multiple anti-anginal medications selected from one or more of the following three classes of drugs: nitrates, β-blockers, and calcium channel antagonists. A minimum of 404 patients may be enrolled. Up to 50 investigational sites may be used for this study. After determination of an individual subject's final eligibility, the patient may be enrolled, randomized, into the study. Randomization of patients will occur in equal proportions to one of the four treatment groups: placebo (saline) or 2, 200, or 2000 µg pVGI.1 (VEGF2). Study drug will be administered to patients by injection into the myocardium by using a cardiac catheter advanced percutaneously, transvalvular into the left ventricle. All patients will remain on their pre-study regimen of anti-anginal medications unless modifications are required because of intolerability. After dosing patients will remain in hospital for 24 hours observation and *may* remain in hospital for up to three days. Following discharge from hospital the patients will return at weeks 1, 2 & 4 and months 2, 3, 6, 9, and 12 of the post-treatment period for follow-up efficacy and safety assessments. Following the formal Post-treatment evaluation period patients will have annual follow-up evaluations (15 years). The long-term follow-up evaluations phase will consist of annual evaluations to be completed by either the Investigator or the patient's personal physician.

If at the Month 6 visit the patient has not shown clinically significant improvement ("treatment failure") in exercise tolerance and at least one other significant indicator of degree of disease, such as the SAQ, CCA Class, or no change (decrease) in the frequency of use of SL nitroglycerine, then the Investigator may request that the patient may be considered for reentry into the protocol as an open label patient who will receive a dose of pVGI.1(VEGF2) to be determined by the Data Safety Monitoring Board charter.

Safety will be assessed by evaluation and comparison of baseline and follow-up parameters, to include, physical examination, 12-lead electrocardiogram, transthoracic echocardiogram, vital signs (temperature, blood pressure, heart rate and respiration), hematology, clinical chemistry, urinalysis, concomitant medications, plasma VEGF-2 concentrations, serum antibody to VEGF-2, and the monitoring of adverse events. The long-term (15 year) follow-up of patients will assess changes from baseline observed in the patient's health as detected during routine annual follow-up visits to the physician. During these visits the investigator will request from the patient information regarding various routine tests the patient may have had during the course of the previous year. These long term follow-up data points may include the results of any tests the patient may have had during the preceding year, i.e. X-rays, ophthalmologic evaluations, PAP smears, PSA test results, laboratory tests. In addition to these tests the investigator should also complete a physical examination of the patient and obtain information regarding any medical events that may be classified as Serious Adverse Events by FDA or NIH definition as found in the regulations.

The primary efficacy endpoint for this study is the change from baseline in exercise duration (Bruce Protocol) when assessed at Month 3. Secondary efficacy endpoints, also assessed at Month 3, include change from baseline in angina class; change from baseline in functional status as assessed by using the Seattle Angina Questionnaire; and change from baseline in myocardial perfusion at rest and under pharmacological stress as determined by using single photon emission computed tomography (SPECT).

The primary analysis will begin with a one-way analysis of variance of treatment effects. If the treatment effect is found to be significant ( $p < 0.05$ ), then a step-down procedure for making multiple one-sided pair-wise comparisons against a control will be employed to determine if one or more of the pVGI.1 (VEGF2) doses has an effect better than placebo: Primary efficacy analysis will be conducted on the intent-to-treat population with the baseline value carried forward for any patients missing Month 3 data. Sample size for the primary endpoint was estimated in an iterative manner using a one-sided Dunnett's Test at an alpha level of 0.05 as an approximation to the actual step-down procedure. A sample size of 101 patients per treatment group has greater than a 90% power to detect a 75-second difference and an 80% power to detect a 60-second difference in change from baseline exercise duration between any pVGI.1 (VEGF2) dose group and placebo. Enrollment may be increased based on a blinded administrative analysis of the variance in ETT results. As non-primary assessment of exercise duration, an analysis of covariance model will be used to further examine dose effects on change from baseline. The model will include terms for the treatments, the baseline value, and center. The treatment-by-baseline value and treatment-by-center effects will be investigated.

One of the secondary efficacy endpoints will be the proportion of patients who have a 2 or more class reduction from baseline in angina class. This endpoint will be analyzed by using a logistic regression model that includes terms for treatment, baseline value, and center. Contrasts representing the pair-wise comparisons between each pVGI.1 (VEGF2) dose group and placebo will be tested according to a second step-down procedure to determine if one or more doses has an effect on change from baseline in angina class. Patient functional status will be analyzed by using analysis of covariance in a model that includes terms for treatment, baseline value, and center. If a treatment effect is found to be significant ( $p < 0.05$ ), then Dunnett-Hsu methods will be used to compare results between each of the individual pVGI.1 (VEGF2) dose groups and placebo. The third secondary endpoint, myocardial perfusion, will be analyzed and reported with regard to changes in perfusion defects by using a discrete 0 to 4 scale for each of 20 left ventricular segments. The change from baseline in the sum of these numbers will be analyzed using analysis of covariance. The model will include terms for the treatments, baseline score, baseline count of abnormal segments, and center. The treatment-by-baseline value, treatment-by-baseline count, and treatment-by-center effects will be investigated. If the treatment effect is found to be significant ( $p < 0.05$ ), then Dunnett-Hsu methods will be used to compare results between each of the individual pVGI.1 (VEGF2) dose groups and placebo.

Interim Safety analysis are planned to occur after approximately 50, 100 and 250 patients have been enrolled in the trial and have completed their 2 week assessments. Enrollment of new patients may be suspended following randomization of patient 50 to 55, 125 to 130 and 250 to 255, until such time as the Data Safety Monitoring board has completed its evaluation of the interim safety data.

## 2) NON-TECHNICAL ABSTRACT OF THE CLINICAL PROTOCOL

Cardiac angina (chest pain) is the result of inadequate blood flow to the heart muscle, a condition called myocardial ischemia. Myocardial ischemia is most often caused by coronary artery disease (CAD). Cardiovascular disease is the number one cause of death in the United States of America, and most cardiovascular deaths are due to CAD. Medications, angioplasty and/or coronary artery bypass graft (CABG) surgery may be sufficient to reduce myocardial ischemia and thereby relieve chest pain in some patients. These methods are sufficient and suitable for many patients who have less advanced CAD. It is for the benefit of the patient with more advanced CAD, patients that are not suitable candidates for the more traditional treatments, that the Sponsor is investigating the use of gene therapy. It is hoped that this treatment will effectively increase blood flow within the heart of the patient with few remaining therapeutic options. Preliminary trials indicate that this specific gene therapy may have been, in some cases, extremely effective. This trial will help to define the dose of medication to use in the patient and to further support the early evidence that correctly selected patients may benefit from this therapy.

This is a double-blind, placebo-controlled study of the plasmid deoxyribonucleic acid (pDNA) named pVGI.1(VEGF2) administered to human subjects. The pDNA contains the gene for one normal human protein, vascular endothelial growth factor 2 (VEGF-2). A minimum of 404 patients may be enrolled in this study at up to 50 study sites. This study will investigate the individual patient's response to one of three doses of pDNA, either 2, 200 or 2000 µg or to a placebo dose of salt. The primary patient response to be evaluated is the patient's ability to exercise. Selected other responses and patient safety will also be evaluated. The dose of pDNA will be injected directly into the patient's heart muscle using a per-cutaneous, cardiac injection catheter. For this study, the locations of the injection points within the heart will be selected by using a special cardiac mapping procedure being co-developed with this cardiac catheter and plasmid medication. Patients will be eligible for treatment only if they have advanced angina (Canadian Cardiovascular Society class III or IV angina). Furthermore, patients will only be eligible for this study if they are determined to be unable to undergo additional traditional revascularization procedures.

The treatment will involve using a catheter to deliver deoxyribonucleic acid (DNA), or genetic material, into the heart. Once inside the heart muscle, this DNA may direct the muscle cells to make a single protein called vascular endothelial growth factor 2 (VEGF-2). The growth factor is a protein that has been shown to cause growth of new blood vessels under a variety of conditions. Laboratory experiments have suggested that VEGF-2 gene therapy may be used to grow new vessels in animals whose arteries have been surgically blocked. Additionally, VEGF-2 gene therapy is being investigated to increase blood flow and reduce resting leg pain (i.e., ischemic rest pain) in the feet or legs of patients with critical limb ischemia, or leg pain due to decreased blood flow in legs due to blocked arteries.

The Pre-treatment, Treatment and a Post-treatment Phases of this study will last up to 13 months. Following the last study visit patients will be required to have annual health evaluations for up to 15 years as required by federal regulations. Interim Safety analysis are planned to occur after approximately 50, 100 and 250 patients have been enrolled in the trial and have completed their 2 week assessments. Enrollment of new patients may be suspended following randomization of patient 50 to 55, 125 to 130 and 250 to 255, until such time as the Data Safety Monitoring board has completed its evaluation of the interim safety data.

Patients who do not show satisfactory medical improvement of their angina after the first dose injected ("treatment failure") may have their cases individually evaluated by a panel of experts. The panel will decide if it is in the patient's best medical interest to be dosed post six-months with study medication. The panel will also determine with what dose of plasmid DNA the individual "treatment failure" patient may be treated. By this mechanism the sponsor feels that the best interest of all the patients, especially those who received a placebo dose as the initial study dose, will be served.

In summary, the Sponsor is investigating the possibility that the delivery of VEGF-2 DNA into the myocardial muscle will result in the development of new blood vessels and thereby increase the blood supply to the heart and reduce chest pain.