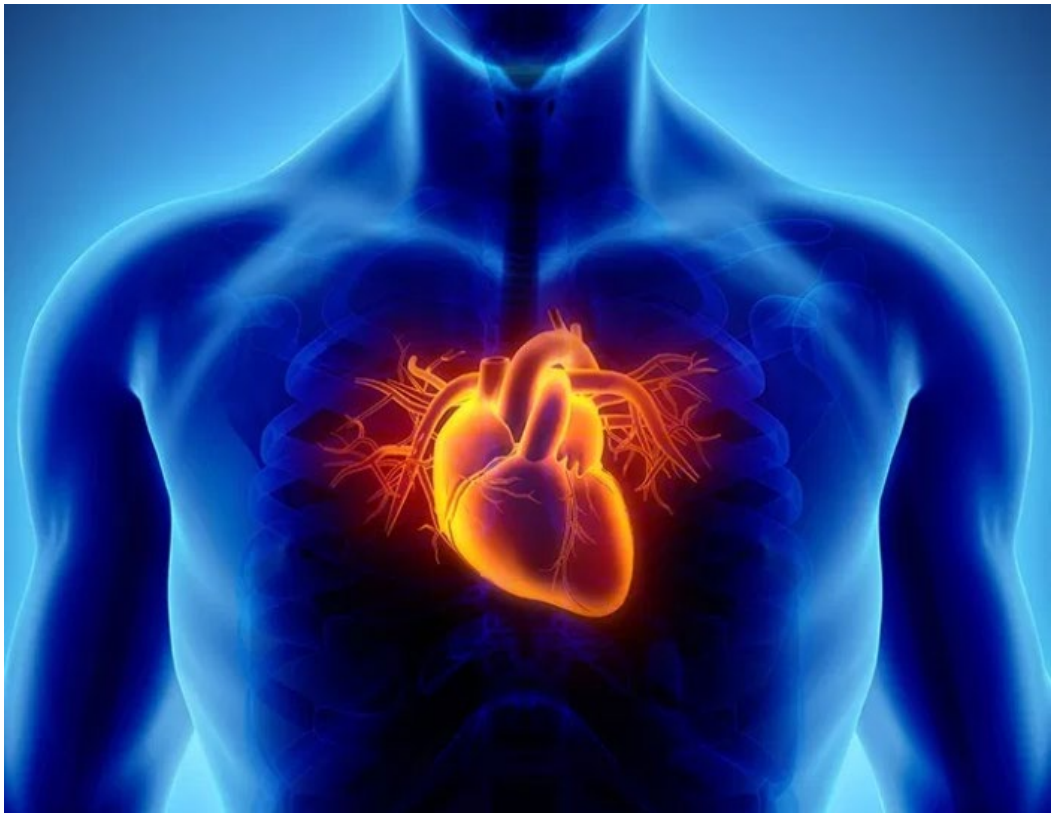
ZHITTYA
REGENERATIVE MEDICINE INC.

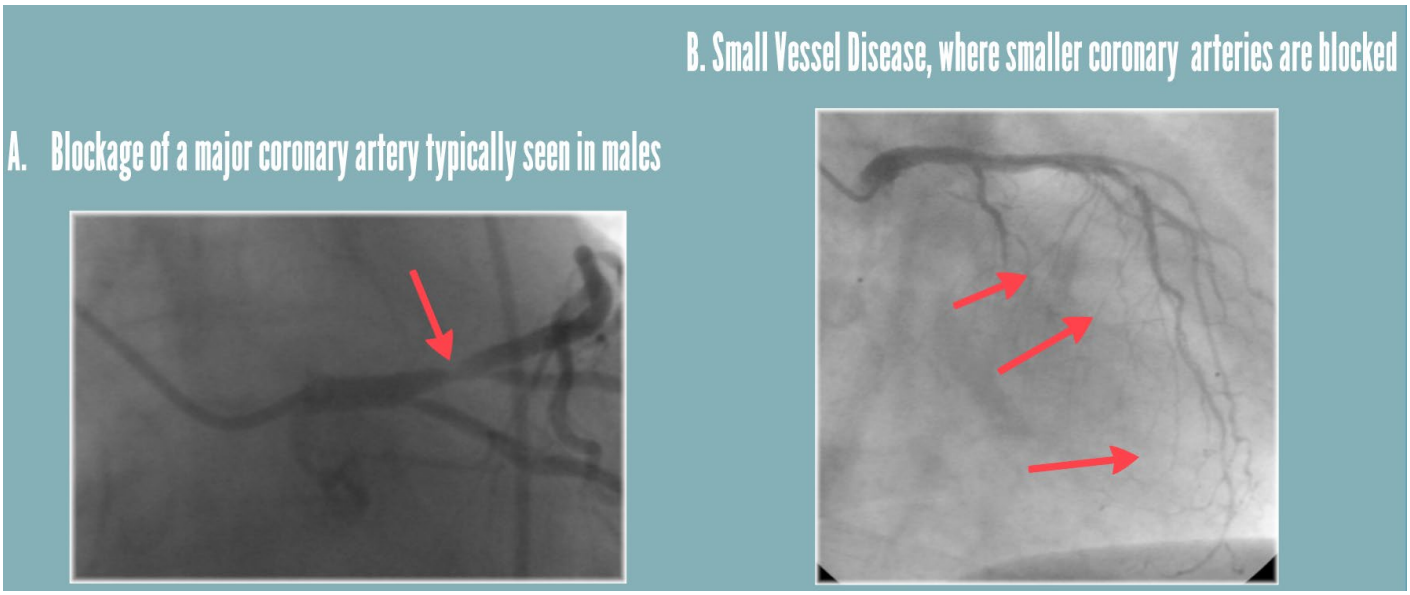
Breakthrough Treatment of Severe Coronary Artery Disease with FGF-1: Results from Four Human Studies



Introduction: FGF-1 for the treatment of no-option coronary artery disease

In the U.S. it is estimated that up to 500,000 subjects suffer from severe CAD for which no medical or surgical options exist, a group which has been referred to as "No-Option Heart Patients". The pathology underlying this disease is depicted in Figure 1 below. For over a decade we have lived with the promise that therapeutic angiogenesis, defined as the growth of new blood vessels in tissues damaged by poor blood perfusion, would provide a lasting clinical benefit to patients suffering from severe CAD.

Figure 1: *Coronary artery angiogram of a no-option heart patient. On the left the arrow points to a coronary artery that is severely occluded. On the right the three circles and arrows point to completely blocked vessels resulting in ischemic heart muscle.*



Numerous successful protein, gene and cell-based angiogenesis studies in early stage clinical trials have not been followed by positive efficacy data in later stage trials which have been blinded and placebo-controlled [1-14].

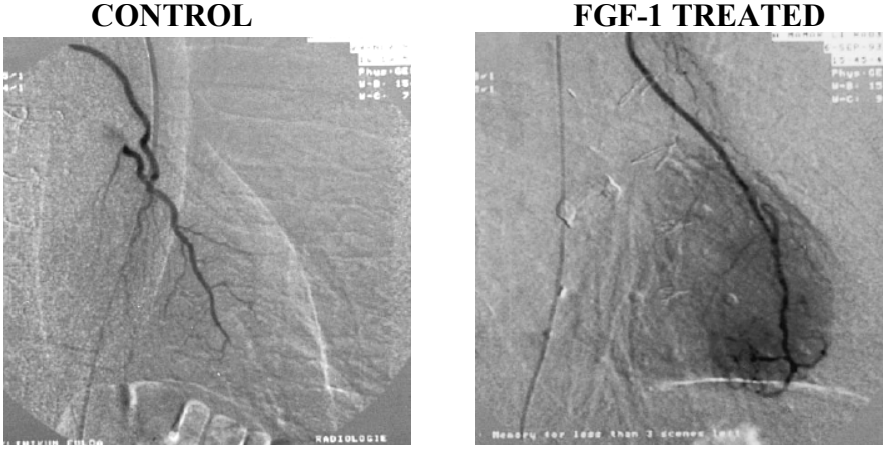
Early clinical studies with protein-based therapeutics [1-5, 12-14] largely focused on the intravenous or intracoronary administration of a particular growth factor to stimulate angiogenesis in the affected tissue or organ. Most of these trials did not achieve statistically significant improvements in their clinical endpoints which ultimately led to an abandonment of this approach and a widespread belief in the field that protein therapy, especially with a single agent, was not a viable option to treat ischemic cardiovascular disease.

However, the failure of gene or cell-based therapy to deliver, as of yet, a suitable treatment choice for diseases resulting from poor blood flow, has led to a resurgence of interest in returning to protein-based therapy to stimulate angiogenesis. Lessons learned from earlier protein-based studies, which indicated that an intravenous or intracoronary delivery of the protein was not

efficacious, have led to completed and ongoing clinical studies in which the angiogenic protein is injected directly into the beating ischemic heart. As shown in Figure 2 below, when this approach is taken the growth of new blood vessels in the ischemic heart muscle can be clearly visualized.

Figure 2 shows a coronary angiogram from a patient with severe coronary artery disease before and after the localized administration of the potent angiogenic growth factor, human FGF-1. An example of the robust "blush" of angiogenesis is seen in the figure where an angiogram taken 12 weeks after FGF-1 injection reveals dense capillary growth around the site of FGF-1 injection into the ischemic heart wall (9). This leads to enhanced perfusion into the ischemic muscle which can be quantitated by a number of clinical tests that will be discussed in further detail below.

Figure 2: *Coronary angiogram in a patient with severe CAD before and 12 weeks after the local administration of human FGF-1 into the ischemic heart wall. A "blush" of new blood vessels can be seen around the site of FGF-1 administration (from Schumacher et.al.; ref 9).*



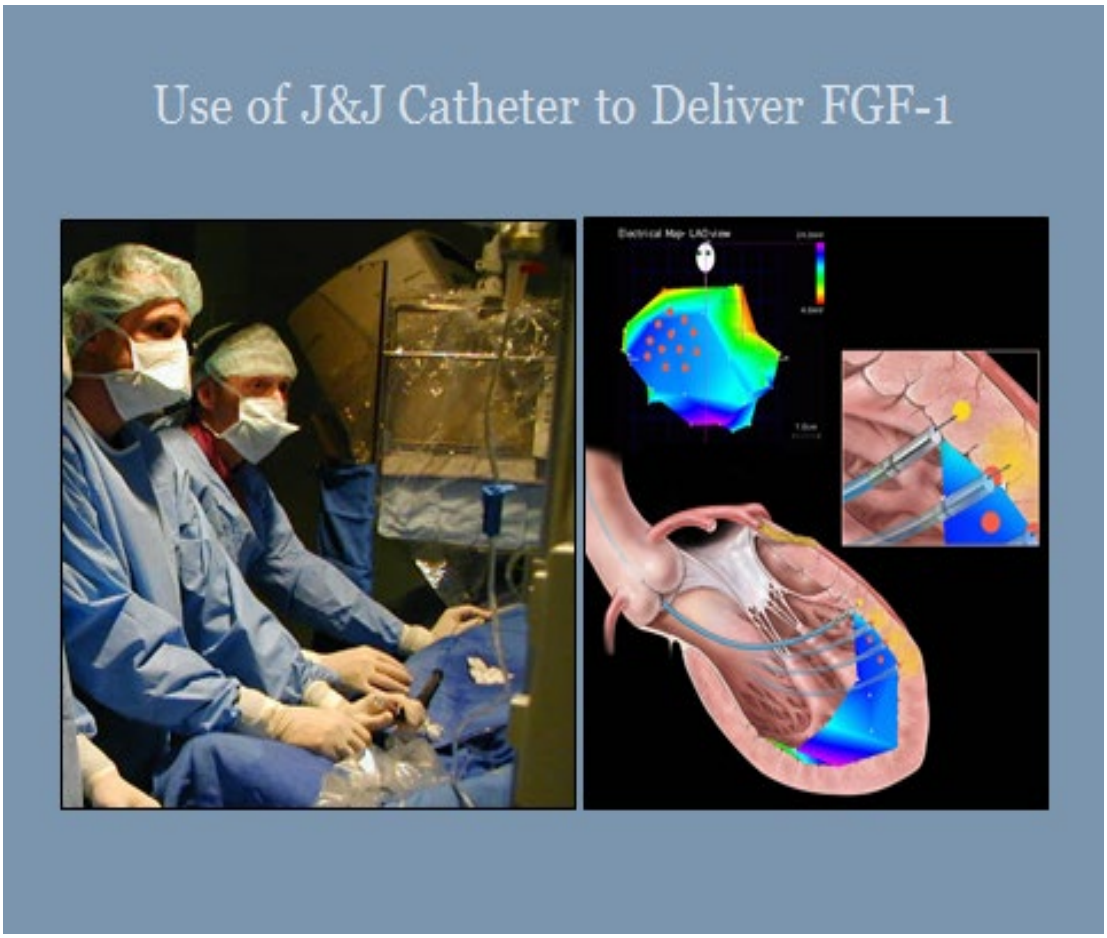
In a US FDA-authorized Phase I clinical trial carried out by the Dallas-based biotechnology company, Cardiovascular BioTherapeutis, Inc., FGF-1 was injected into the hearts of no-option heat patients and it was established that there was statistically significant improvement ($p<0.05$) in 3 important clinical parameters that are used to measure the efficacy of these drugs, as shown in Figure 3 below (11, 17). These analytical tests include from left to right, anginal class, anginal scores and time on the treadmill. The treadmill test is the gold standard efficacy test for this class of patients and is the primary endpoint generally accepted by the FDA for a pivotal Phase III clinical trial.

Zhittya's Drug Development Program for Coronary Artery Disease

Zhittya Regenerative Medicine, Inc. (Zhittya) is developing human FGF-1 (16) as a protein-based therapy which will be directly injected into the myocardium through a minimally-invasive surgical process. The Cordis (a Johnson & Johnson Company) NOGA MyoStar catheter mapping and injection system will be used to obtain access to the heart via a femoral artery catheterization, to

visually target the ischemic areas of the myocardium for real-time injection of FGF-1. A schematic representation of the NOGA Myostar injection catheter is shown in Figure 4 on the following page below.

Figure 4: *A schematic representation of the NOGA Myostar injection catheter. On the left side vascular surgeons thread the catheter up the femoral artery and into the patient's heart. Prior to injection of FGF-1 into the inside wall of the heart, ischemic regions are mapped by the NOGA system and on the right side of the figure ischemic heart tissue is depicted in blue. A series of FGF-1 injections (depicted as small orange circles on the right side of the figure) are made within the ischemic areas of the heart. The procedure can be performed in an outpatient catheterization lab and takes about 30 min to perform.*



It is critically important that the angiogenic growth factor be directly injected into the myocardium to get a robust angiogenesis effect. Early trials in which the growth factor was administered intravenously or into the coronary arteries failed, as the therapeutic agent was rapidly flushed out of the heart and then eliminated from the body within hours. Previous work has established that

when FGFs are injected directly into heart muscle the molecule stays resident in tha tissue for 3-4 days. Zhittya's approach is unique, allowing for the targeted delivery of a precise amount of FGF-1.

Likewise, gene therapy vectors introduced new variables for DNA delivery and expression levels, leading to a lack of precision and consistency in drug delivery, and resulting in poor outcomes, serious adverse events, and safety concerns.

Basic scientific, preclinical and early-stage clinical studies support the angiogenic potential of FGF-1 in stimulating the growth of new functional and stable blood vessels, including in the human myocardium (8-11). For patients suffering from ischemic heart disease as a result of blocked heart vessels, FGF-1-induced angiogenesis results in increased perfusion, leading to patient freedom from angina, improved physical function and quality of life. Such improvements in cardiac function should result in reduced frequency and severity of heart attacks and extend the lives of these patients.

Clinical Trial Results: Four previous studies established the efficacy of FGF-1 to treat severe CAD in no-option heart patients

Below four separate clinical trials that used FGF-1 to treat severe coronary artery disease will be reviewed. The data shown here has been collected from publicly available documents including academic publications in the medical literature, or publications, press releases and investor solicitations that have been put into the public domain by CardioVascular Bio-Therapeutics, a Dallas-based biotechnology company.

1. First German trial: FGF-1 Injection in Combination with a Bypass Procedure

The first angiogenesis trial in humans was performed in Germany by Dr. Thomas Stegmann of the Department of Thoracic and Cardiovascular Surgery, Fulda Medical Center, Fulda, Germany (9). The study was an open-label, randomized, placebo-controlled study in patients receiving by-pass surgery for severe coronary artery disease.

Forty subjects were randomized and twenty patients received 10 µg FGF-1/kg body weight with the placebo group receiving a similar quantity of heat-inactivated FGF-1.or a placebo containing vehicle plus an equivalent amount of heat-denatured FGF-1.

In all 20 of the patients that received active FGF-1, a blush of new blood vessels could be observed on angiograms. Remarkably, these blood vessels could be still seen as patent, functioning vessels at year 3 following the treatment

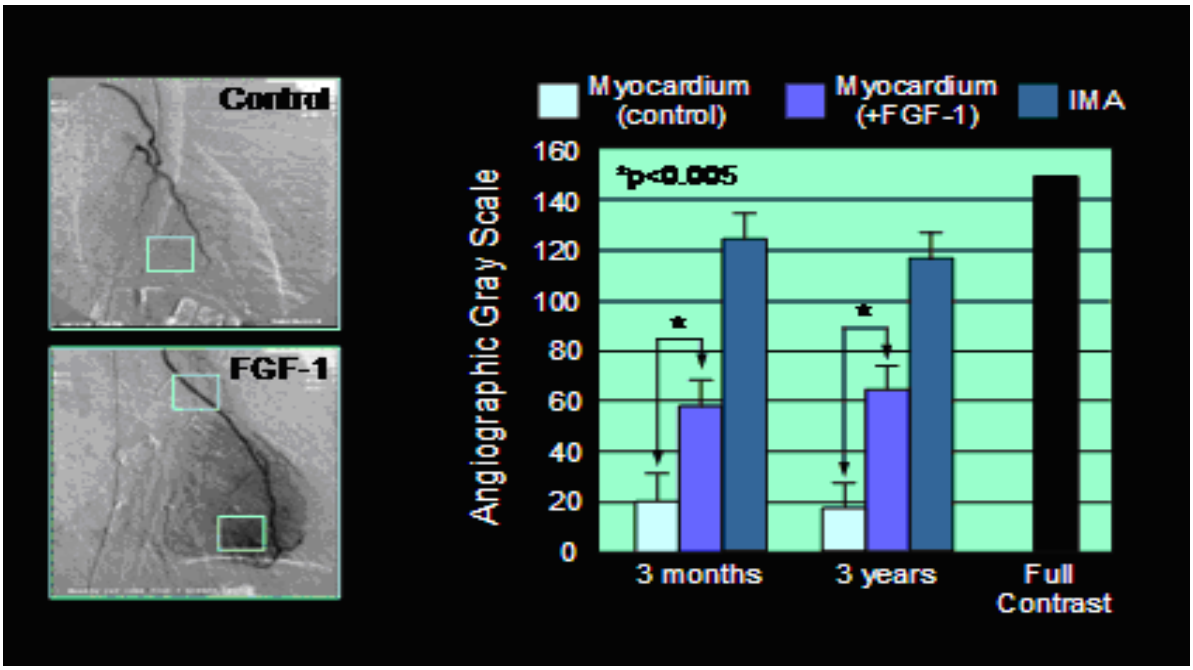
As shown in Figure 5 below, quantification of gray levels in the angiograms in the region of the heart that FGF-1 was injected revealed an increase in microvascular perfusion at 12 weeks compared to placebo control-treated subjects, reflecting an increase in capillary density and blood

flow in and around the site of FGF-1 injection. The vascular density of the FGF-1 arm was statically greater than controls at three months.

No adverse events were observed that were considered to be directly related to FGF-1 treatment at 3 months or 3 years.

This study demonstrated that intramyocardially-injected FGF-1 into the severely ischemic heart can induce robust angiogenesis and is safe. All patients treated with FGF-1 experienced the growth of new blood vessels at the site of treatment. As compared to patients receiving a placebo injection, FGF-1-treated patients experienced a statistically significant increase in capillary density that was stable at three years post-treatment (9).

***Figure 5**: Quantification of angiographic gray levels in FGF-1 injected subjects revealed an increase in microvascular perfusion at 12 weeks and 3 years compared to placebo control-treated subjects. The vascular density of the FGF-1 arm was statically greater than controls at both three months and 3 years.*



2. **Second German trial: FGF-1 as Sole therapy for "No-Option" heart patients**

Again, this trial was conducted by Dr. Thomas Stegmann of the Department of Thoracic and Cardiovascular Surgery, Fulda Medical Center, Fulda, Germany. It was conducted in patients who were not amenable to re-vascularization surgery and were considered "no-option" patients. Because the FGF-1 was delivered via a mini-thoracotomy, considered an invasive procedure, no

placebo group was included in this study. The main objectives of the study were to determine the safety and tolerability of FGF-1 injection into the heart and if the patients showed clinical benefit at 12 weeks as assessed by perfusion measurements by SPDCT and improve exercise performance on the bicycle.

Twenty no-option heart patients were enrolled and treated in the study. with three-vessel coronary artery disease who met inclusion criteria were enrolled. Patients received up to 3 injections of FGF-1 into areas of the heart identified as ischemic, either through angiograms or SPECT perfusion analysis with ^{99m}Tc-sestamibi.

SPECT perfusion analysis of FGF-1-treated areas was done under both rest and stress conditions using a 17-segment analysis procedure. Exercise performance was done by a standardized bicycle exercise test.

For safety, serum tumor markers were followed, along with retinal photography to ascertain if any neo-angiogenesis was occurring in the eye. Cardiac enzymes indicating any heart damage were also followed.

Figure 6: *SPECT analysis under both resting and stress conditions. Data was collected prior to FGGF-1 injection and then again at 45 and 90 days post-operatively. Statistically significant improvement was seen over baseline at both 45 and 90 days after FGF-1 injection.*

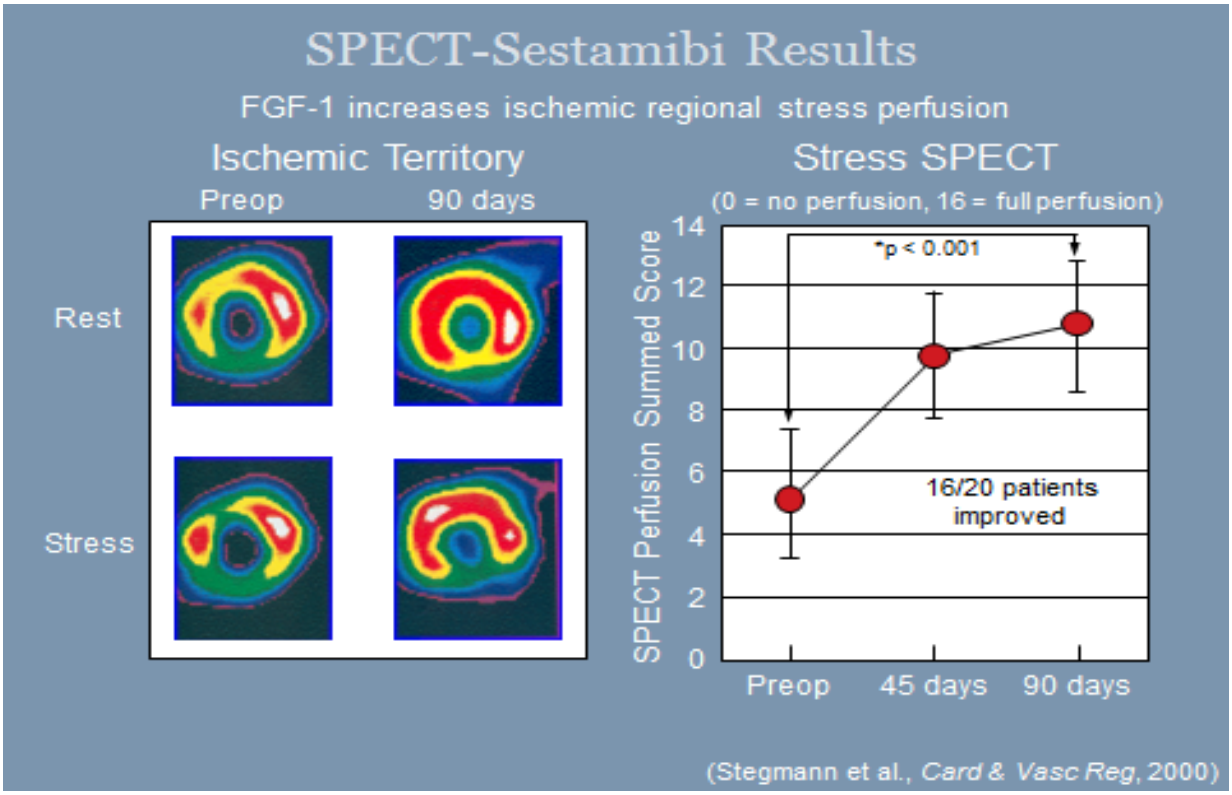
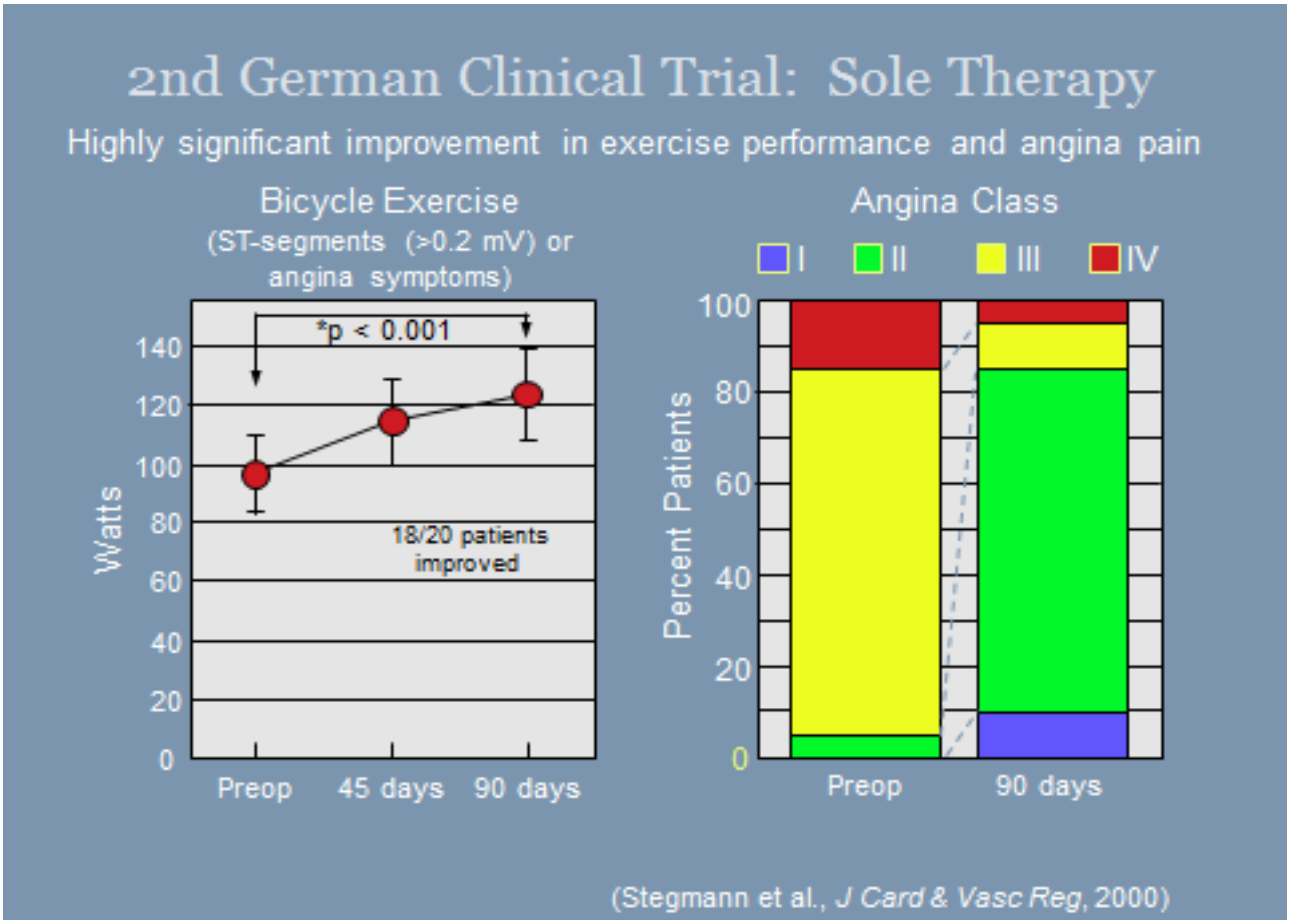


Figure 6 above shows the result of the SPECT analysis before and after treatment with FGF-1. At day 90 following FGF-1 injection, 21 out of 25 treated areas (84%) and 16 out of 20 patients (80%) experienced substantial increases in myocardial perfusion as indicated by SPECT. These data were supported by repeat standard coronary angiography that measured increased capillary density at all FGF-1-treated sites in all patients.

In exercise testing, an increase in maximal working capacity was demonstrated in 16 out of the 20 patients (80 %) following FGF-1 treatment (see Figure 7 below).

Figure 7: *Efficacy data showing an improvement in exercise testing (left panel) and angina pain scores (right panel).*



Postoperative ECGs and values for cardiac isoenzymes remained unchanged and showed no evidence of myocardial ischemia in any of the patients.

In all patients the levels of all tumor markers continued to stay in the normal range for the duration of the study; no elevation was seen in any of the tumor markers evaluated. Also, the serial

ophthalmoscopic controls in all patients definitively excluded any change of the status of the retina, the cornea, and the corpus vitreum. There was no indication of additional vascularization in these tissues.

This study demonstrated the safety and feasibility of intramyocardial FGF-1 protein delivery as the sole therapy for "no option" heart patients. Patients treated with direct myocardial injection of FGF-1 experienced a reduction in angina symptoms and a statistically significant increase in exercise capacity. These improvements were most likely the result of an observed increase in capillary density and improved myocardial perfusion following treatment by FGF-1 at the treatment sites that displayed ischemia. There were no deaths or major complications and all laboratory markers remained essentially unchanged throughout the total study course (10).

3. US FDA-authorized Phase I Clinical Trial Studying the Safety and Efficacy of FGF-1 for "No- option" CAD patients

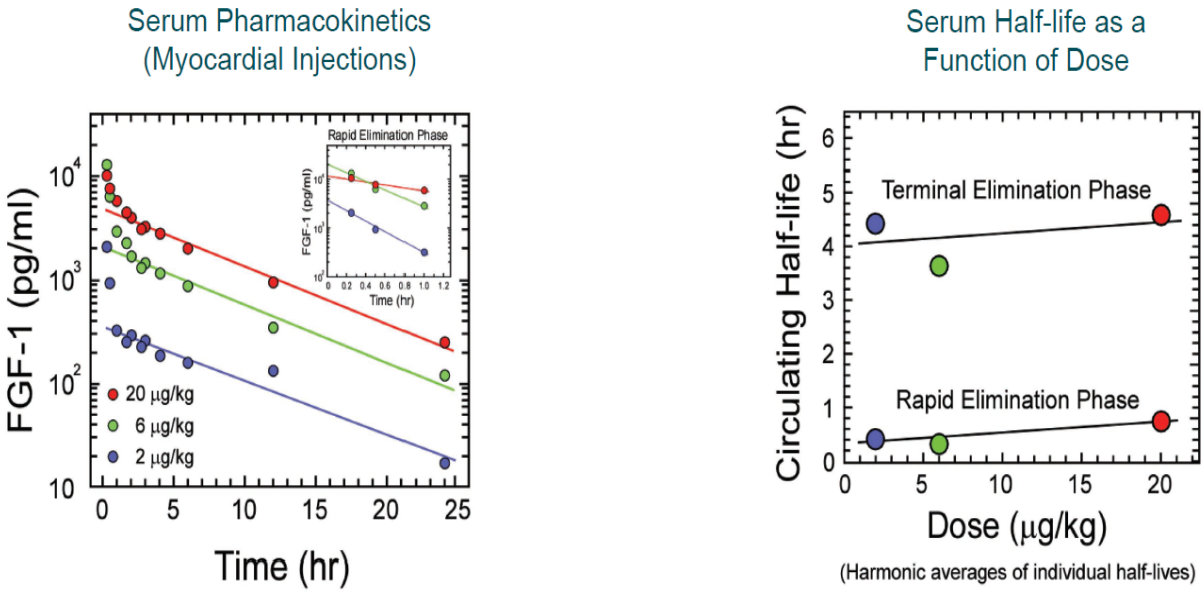
This trial was performed by the Dallas-based biotechnology company, CardioVascular Biotherapeutics, Inc. Twenty-one patients were assigned to one of three different groups, each receiving a different dose of FGF-1 solution: 1, 3, or 10 μg/kg body weight per injection. The study was a Phase I open label study with no placebo group. The drug was administered via mini-thoracotomy for the treatment of "no option" coronary heart disease (11, 17). The primary endpoints were the safety, tolerability, and pharmacokinetics of escalating doses of FGF-1. Effectiveness was assessed by measuring the impact of FGF-1 treatment on myocardial perfusion, exercise tolerance, CCS angina class, and Seattle Angina Questionnaire scores.

Efficacy results from that trial done 12 weeks after the FGF-1 injections showed statistically significant improvement in 3 clinical parameters, including angina pain class, Seattle Angina Score (a second assay of angina pain) and the treadmill test (see Wagoner, et.al.; ref 17).

Pharmacokinetic Analysis of FGF-1 Clearance in Humans

Pharmacokinetic data is presented in Figure 8 below which looks at plots of circulating levels of FGF-1 at different time points for individual patients. It can be seen that FGF-1 concentrations reach peak levels very rapidly within minutes of injection and then decrease rapidly within the first hour post-injection. FGF-1 levels reach near pre-treatment baseline concentrations within 12-24 hours. No patients in any of the dosing groups demonstrated any detectable increase in levels of FGF-1 specific antibodies at either 6 or 12 weeks.

***Figure 8**: Pharmacokinetics of FGF-1_{141} in Patients with Severe Coronary Heart Disease Following Intramyocardial Injections of FGF-1. On the left-hand panel the serum levels of FGF-1 are plotted versus time after injection into the heart. On the right-hand panel the two elimination phases of FGF-1 from the circulation are apparent and include a rapid and a slower (terminal) elimination phase seen for each dose of FGF-1 administered (from Wagoner et al, reference 17).*



Although there were a number of serious adverse events reported throughout the course of the study, none could be directly attributable to FGF-1. This is a very seriously ill population of patients and adverse vents unrelated to the drug treatment were to be expected. All tumor markers remained within normal limits and no significant changes were detected in the ophthalmologic exams (11, 17).

Zhittya's Planned Clinical Studies with FGF-1 in Coronary Heart Disease

Zhittya will first conduct a Phase I trial in no-option heart patients in which the subjects will receive a catheter-administered dose of FGF-1. The study design will be similar to the one published by Wagoner et al (17) with some modifications in the exercise treadmill test. In addition, MRI-based cardiac perfusion analysis may also be added as this technique is gaining popularity with cardiologists as a more sensitive and quantitative measurement of cardiac perfusion in defined areas of the ischemic heart.

Business Opportunity

We believe that once our drug is approved by the US FDA it will become the standard of care to treat coronary artery disease, replacing most PTCA and CABG procedures. We believe our drug will treat over 1,000,000 patients annually in the United States and will have a multi-billion US dollar sales potential. Based upon our pharmacoeconomic analysis, we believe with our drug selling for $20,000 per treatment, it will still deliver a 50% cost savings to payers over present treatments for coronary artery disease.

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