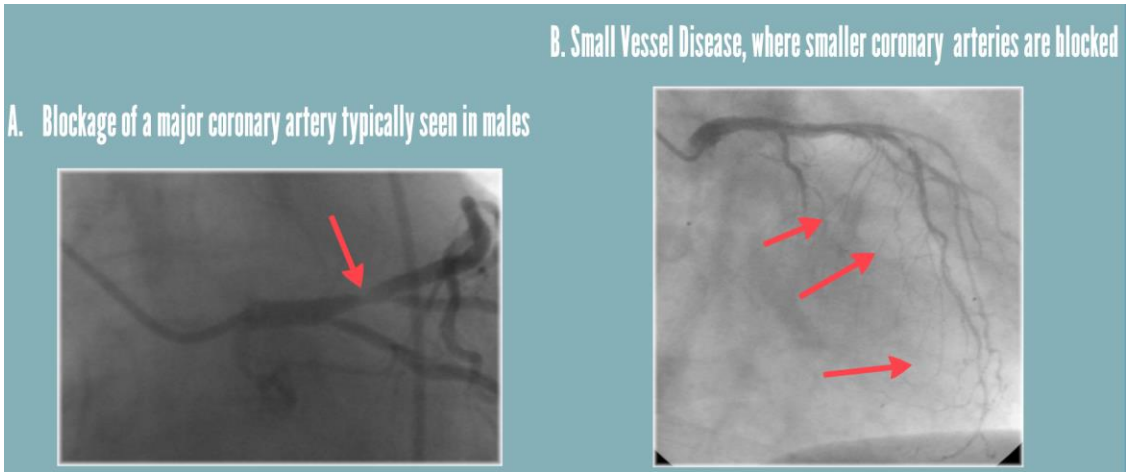
ZHITTYA
REGENERATIVE MEDICINE INC.

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].

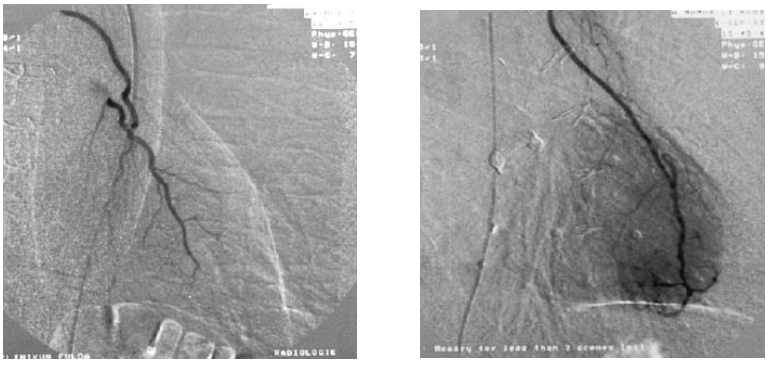
Early clinical studies with protein-based therapeutics [1-5, 12-14] largely focused on the intravenous or intracoronary administration of a particular growth factor to stimulate angiogenesis in the affected tissue or organ. Most of these trials did not achieve statistically significant improvements in 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).*

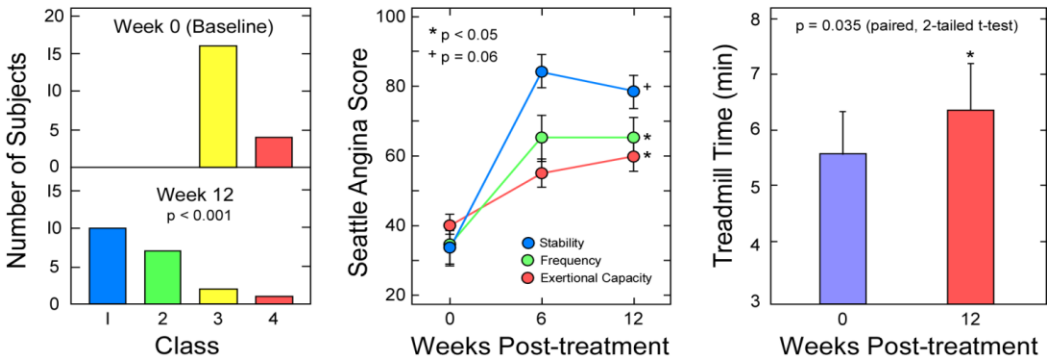
CONTROL **FGF-1 TREATED**



In a US FDA-authorized Phase I clinical trial where FGF-1 was injected into the hearts of no-option heat patients 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.

Figure 3: *Results from a US Phase I clinical trial in which patients with severe coronary artery disease received localized injections of human FGF-1 into their ischemic hearts. Efficacy testing was done 12 weeks after the FGF-1 injections and showed statistically significant improvement in 3 clinical parameters, including from left to right, angina pain class (with class 4 angina being the most severe), Seattle Angina Score (a second assay of angina pain) and the treadmill test (from Wagoner, et.al.; ref 17).*



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.

ZHITTYA's FGF-1 heart program will directly inject a growth factor protein into the myocardium. Past failed attempts by other research groups have used completely different therapeutic models and delivery systems.