

PART 2: NON-TECHNICAL ABSTRACT

The purpose of this clinical research study is to examine the safety and the potential ability of a new study treatment to stimulate the growth of new blood vessels from existing blood vessels (a process called angiogenesis) to improve the flow of blood within an area of the myocardium that is viable, but not amenable to conventional bypass or percutaneous intervention in patients with coronary artery disease who are undergoing elective coronary artery bypass graft (CABG) surgery. This treatment, named Ad2/HIF-1 α /VP16, is a new kind of gene transfer which was developed by the sponsor of this study, Genzyme Corporation. This investigational drug transfers a gene into cells within the patient's myocardium, which cause the cells to produce a modified form of a substance naturally produced by the body called hypoxia inducible factor one alpha (HIF-1 α).

The gene for HIF-1 α /VP16 will be introduced into the cells by using a modified virus called an adenovirus. Adenovirus (Ad2) is a common virus found in human airways and, in its normal state, can reproduce and cause a cold. This virus (Ad2/HIF-1 α /VP16) has been altered so that it can not reproduce. The production of HIF-1 α is a normal part of the patient's cellular response to low amounts of oxygen caused by reduced blood flow. When native HIF-1 α or HIF-1 α /VP16 enters these cells it causes the cells to produce and release growth factors like vascular endothelial growth factor (VEGF) and other substances. These growth factors (called angiogenic growth factors) have the ability to stimulate the growth of new blood vessels from existing blood vessels and, as a result, increase the flow of blood carrying oxygen to these cells.

Genzyme has conducted extensive efficacy, toxicity and biodistribution studies in pigs and rats to support the proposed cardiac ischemia protocol. Results of these studies are summarized in Appendix M-II-B-2-b-(3), Appendix M-II-B-2-d and in the clinical protocol. These studies are as follows:

- Efficacy:
 - Bioactivity of transepicaldial intramyocardial injection in a pig model of chronic myocardial injection.
 - *In vitro* bioactivity studies.

these assessments include laboratory testing for injury to the myocardium, electrocardiograms to monitor for abnormal heart beats or rhythms, and echocardiograms to look for extra fluid next to the heart or changes in the beating of the ventricular wall.

In addition, the study will include assessments (e.g., cardiac nuclear and magnetic resonance scans) to evaluate the extent of Ad2/HIF-1 α /VP16 mediated new blood vessel growth to improve the flow of blood within the selected area of the myocardium. The study will also evaluate potential clinical outcomes for assessing the ability of the Ad2/HIF-1 α /VP16 to increase blood flow in the heart and relieving chest pain (angina pectoris).

Patient status will be monitored for 1 year after receiving Ad2/HIF-1- α /VP16 or placebo during CABG surgery.