

## **PART 2: NON-TECHNICAL ABSTRACT**

Genzyme Corporation is continuing to examine the safety of an experimental gene transfer agent, Ad2/HIF-1 $\alpha$ /VP16, and its ability to stimulate the growth of new blood vessels from existing blood vessels (a process called angiogenesis) in an attempt to improve the flow of blood in the legs of patients with peripheral arterial disease (PAD). Specifically, in this exploratory clinical research study the investigator will use different types of Magnetic Resonance Imaging (MRI) tests to determine whether these types of tests can detect changes in blood flow and chemicals in the leg. These changes may indicate that more oxygen is getting to the leg muscles and may be able to be used to help show if the study drug, Ad2/HIF-1 $\alpha$ /VP16, is having the effect that is desired. The primary goal of the study is to determine if these MRI tests can detect these changes in the legs of patients who receive the study drug versus those who receive placebo.

Patients with severe intermittent claudication (IC) will be enrolled. IC is the stage of PAD in which a patient's walking ability is severely limited, causing pain in the legs upon exercise due to inadequate blood flow to the muscles of the lower limbs. HIF-1 $\alpha$  is naturally produced by the body in response to low tissue oxygen levels and is responsible for turning on several growth factors involved in the angiogenesis process. 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, potentially increase the flow of blood carrying oxygen to these cells.

Although the gene being transferred into the patients in this study, HIF-1 $\alpha$ /VP16, is closely related to natural HIF-1 $\alpha$ , it is not identical to the natural substance produced by the body. Genzyme has genetically altered it so it has certain important biological characteristics that may promote more robust angiogenesis. Any new blood vessels that may form may increase the flow of blood to the muscles in the leg. Increased blood flow to the leg muscles may reduce the pain (claudication) in the legs upon walking.

The altered gene for HIF-1 $\alpha$  will be introduced into the cells by using a modified virus called an adenovirus. Adenovirus Type 2 (Ad2) is a common virus found in human airways. In general, adenovirus infections result in mild cold-like symptoms. More serious infections by an adenovirus can result in bronchitis, croup, and pneumonia. The

adenovirus used in this study has been altered in the laboratory so that it is unable to replicate and thereby unable to cause the above mentioned illnesses.

### **Overview of Proposed MRI Feasibility Study**

The proposed study will explore the use of three types of magnetic resonance imaging (MRI) tests, including magnetic resonance perfusion (MRP), magnetic resonance angiography (MRA) and magnetic resonance spectroscopy (MRS) to determine if these tests can detect changes in blood flow and chemicals in the leg. These changes may indicate that more oxygen is getting to the muscles and may help show if Ad2/HIF-1 $\alpha$ /VP16 is having the effect that is desired. The primary goal of the study is to determine if these MRI tests can detect these changes in the legs of patients with PAD and to see if there are changes in the blood flow or metabolism in the legs 6 months after injections of the study drug. The study will also collect important safety and some clinical information to support the research that is already ongoing. The study will be conducted in a similar patient population as Genzyme's ongoing Phase 2 clinical study (NIH Protocol 0407-661). Only PAD patients with severe IC who can walk between 1 and 12 minutes on a standardized treadmill test before having to stop due to claudication pain, but whose disease has not progressed as far as Critical Limb Ischemia (CLI), will be enrolled.

The study design is a randomized, double-blind, placebo-controlled, parallel-group, single center. Up to 30 patients (15 patients per treatment group) will be randomized into this study in order to achieve a target of 20 evaluable patients. Patients will be enrolled into one of two treatment arms (Ad2/HIF-1 $\alpha$ /VP16 or Placebo). Each patient will receive a single dose of 20 injections (100  $\mu$ L each) of gene transfer or placebo into one leg. The maximal total dose of Ad2/HIF-1 $\alpha$ /VP16 evaluated to date,  $2 \times 10^{11}$  vp, has been selected as the single dose for further evaluation in this feasibility study. This total dose was previously administered as 20 injections to a single limb in the Phase 1 studies and also the highest total body dose in the ongoing Phase 2 study. A placebo group is included in the study to compare safety and efficacy of Ad2/HIF-1 $\alpha$ /VP16 with placebo.

The duration of each patient's participation in the study will be 1 year. Patients will have scheduled follow-up visits (either on-site or via telephone) at Day 1 and Weeks 1, 4, 12, 26 and 52. Within the protocol, specific safety assessments have been included to monitor for potential adverse experiences that could be related to either the adenovirus in which the gene is placed, the HIF-1 $\alpha$ /VP16 gene contained in the adenovirus, the direct injection of the study drug or placebo into the leg muscle, or the progression of the

patient's underlying disease. At these visits, changes from Baseline in physical exams, vital signs, clinical lab tests, and eye examinations will be assessed. All adverse events will be monitored. A detailed summary of cancer screening requirements at screening and follow-up is included in Appendix 1 of Clinical Protocol PADHIF01007.

Following completion of the Week 52 final study visit, all patients will be asked to consider enrolling in a voluntary extended follow-up program in which limited safety data pertaining to mortality, new cancers, and major amputations will be collected annually. This extended follow-up will be under a separate plan and will have a separate informed consent form.

An independent Data Monitoring Committee (DMC) comprised of independent physicians (not conducting the study) will provide an ongoing, expert review of safety data to assure that the risks to study patients are minimized. The DMC can suspend enrollment or request to see unblinded data at any time should safety concerns arise at any time during the study.

Please refer to **Part 4** of this application for the complete Clinical Protocol PADHIF01007.