

2. NON-TECHNICAL ABSTRACT

The purpose of this Phase 2 clinical research study sponsored by Genzyme Corporation is to examine the safety of an experimental gene transfer agent, Ad2/HIF-1 α /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, this study will enroll patients with severe critical limb ischemia (CLI), a severe form of PAD characterized by pain while at rest, and/or, with skin ulceration.

CLI is a significant unmet medical need because amputation is currently the only therapeutic option for patients whose "last ditch" revascularization procedure for limb salvage has failed. The quality of life in these patients is very poor. Rest pain frequently occurs during the evening when the patient lies supine and significantly alters the patient's ability to sleep. Painful non-healing ulcers often occur on the toes or other sensitive areas of the foot or ankle. Many patients with these types of ulcers need crutches, canes and/or a boot to be able to walk and some are limited to a wheelchair.

HIF-1 α 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 α /VP16, is closely related to natural HIF-1 α , 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, potentially alleviating pain symptoms.

The altered gene for HIF-1 α 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 abovementioned illnesses. Genzyme conducted extensive pre-clinical studies in animal models to test for safety and preliminary efficacy before initiating the Phase 1 studies in patients with CLI.

2.1 Initial Phase 1 Studies for PAD/Critical Limb Ischemia (CLI)

The first Ad2/HIF-1 α /VP16 clinical study for the PAD indication was a Phase 1, randomized, double-blind, placebo-controlled, dose-escalation study conducted in patients with critical limb ischemia (CLI), a severe form of PAD characterized by rest pain and/or non-healing tissue necrosis non responsive to standard measures of care (NIH Protocol Nos. 9907-327/-328/-329). This study, which was conducted at five clinical sites in the United States between October 1999 and June 2003, involved a total of 34 patients who received Ad2/HIF-1 α /VP16 gene transfer.

Overall, the results from the PAD Phase 1 program in the CLI patients showed Ad2/HIF-1 α /VP16 to be well tolerated. Other than mild to moderate injection site reactions, no adverse drug reactions have been identified in these studies. No safety problems emerged that would prevent Ad2/HIF-1 α /VP16 from being tested further in patients with PAD. Refer to the Confidential Additional Information, which accompanies this application, for an integrated safety summary of the Phase 1 study. Although the Phase 1 study (total of 38 patients, 34 of whom received Ad2/HIF-1 α /VP16) was not intended to determine if the gene transfer works, some patients demonstrated clinical improvements of rest pain resolution and complete ulcer healing. However, others had worsening of their symptoms and required amputation.

2.2 Ongoing Phase 2 Study for PAD/Intermittent Claudication (IC)

Genzyme then began a Phase 2 clinical study evaluating Ad2/HIF-1 α /VP16 in a different patient population than the Phase 1 studies. This ongoing Phase 2 study currently is enrolling patients with severe intermittent claudication (IC), which 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. These patients can only walk between 1 and 10 minutes before having to stop due to claudication pain, but whose disease has not progressed as far as CLI. The primary goals of the study are to evaluate safety measures throughout the study and to evaluate if patients have improvement in their walking ability 6 months after receiving the study drug.

The study design is a randomized, double-blind, placebo-controlled, parallel-group, multi-center, Phase 2 dose-selection study. Seventy-five patients will be enrolled into each of 4 study drug groups (3 groups of Ad2/HIF-1 α /VP16 gene transfer and 1 placebo group) for a total of 300 patients overall. Three different doses of Ad2/HIF-1 α /VP16 gene transfer are being studied. The dose range was previously tested in animals and in the Phase 1 human studies. A placebo group is included in the study to compare safety and efficacy of different doses of Ad2/HIF-1 α /VP16 with placebo. Each patient will receive a single set of 20 injections (100 μ L each) of gene transfer or placebo in one administration to each leg for a total of 40 injections.

The duration of each patient's participation in the study will be two years. Thereafter, under a separate program, patients may be followed in accordance with national guidelines for long-term follow up for gene transfer studies.

The first patient received investigational product in February 2005. To date, there have been two treatment emergent SAEs reported from the same patient, "right foot cellulitis" and "toe ulceration" both of which were considered Unrelated to the study drug by the Principal Investigator.

An independent Data Monitoring Committee (DMC) conducts quarterly safety reviews of the cumulative SAEs and adverse vascular events. The DMC chose not to conduct a Q2 2005 review as no SAEs had been reported during that time. The DMC's Q3 review occurred in early October and preliminary results of this review indicated no concerns regarding the SAEs reviewed; a written report is pending. The first interim DMC review is scheduled to occur when the sixtieth patient is randomized and has completed 4 weeks of follow-up. The DMC will be unblinded for this first interim review which will consist of aggregated safety data. This is expected to occur in early 2006. Further randomization will be paused at that time pending DMC review and authorization to proceed, as described in the study protocol. Thereafter, the DMC will continue to conduct quarterly safety reviews focused on cumulative SAEs and adverse vascular events. Further interim safety reviews will be conducted after each additional cohort of 60 patients enrolled and complete 4 weeks of follow-up. Patients will continue to be randomized during the quarterly DMC safety reviews.

2.3 Proposed Phase 2 Study for PAD/Critical Limb Ischemia (CLI)

Genzyme now is continuing with its clinical development of Ad2/HIF-1 α /VP16 into Phase 2 for the critical limb ischemia (CLI) indication. The results from the Phase 1 CLI study show that Ad2/HIF-1 α /VP16 has been well tolerated at doses ranging from 1×10^8 to 2×10^{11} virus particles (vp) and that future clinical trials are warranted for this indication.

Specifically, Genzyme is proposing to evaluate Ad2/HIF-1 α /VP16 in patients with CLI who have either no standard revascularization procedure or have only a poor revascularization option which represents a “last ditch” effort to salvage the limb and avoid amputation. There is a significant unmet medical need in these patients because major amputation is currently the only therapeutic option for no option patients and in those where revascularization procedures have failed.

As with the Genzyme Phase 2 IC study, efficacy endpoints which have been selected for the study have been established by the medical community and regulatory guidelines. These endpoints are focused on the clinical status of these patients with advanced PAD and include the resolution of rest pain, complete or partial healing of ischemic ulcers, and incidence of treatment failure. This study will enroll a total of 90 patients with 45 patients receiving an Ad2/HIF-1 α /VP16 dose of 2×10^{11} virus particles and 45 patients receiving placebo. The study drug will consist of a single dose administered by 20 intramuscular injections to the lower limb most affected by PAD. The duration of each patient’s participation in the study will be two years. The protocol includes specific safety assessments to monitor for potential adverse experiences that could be related to either the adenovirus in which the gene is placed, the HIF-1 α /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.

The primary endpoint for this study is a clinical composite where success is defined as the patient is alive, with the index limb (i.e., no major amputation) and has at least partial healing of the target ulcer (i.e., at least 30%) and/or complete resolution of rest pain. Other endpoints include additional composite endpoints for treatment success or failure and independent assessments of ischemic ulcer healing, rest pain reduction, ankle brachial index, and quality of life.

As with the Phase 2 IC Study, Genzyme has included interim safety checks to closely monitor safety throughout the conduct of the Phase 2 CLI study. An independent Data Monitoring Committee (DMC) will provide an ongoing, expert, independent review of safety data to assure that the risks to study patients are minimized. Specifically two analyses will be performed (1): an assessment of aggregated safety data only for the first 30 patients completing 4 weeks of follow-up, and (2) an interim assessment of the first 60 patients completing 6 months of follow-up. Given the assumption of a 1 year recruitment period in the study, the first review (for safety) may occur approximately 5-6 months after the study starts, and the second interim review may occur approximately 14-15 months after the study starts. The DMC chairperson may schedule unplanned safety reviews at any time during the study, if necessary. The DMC may recommend suspension of enrollment in the study to evaluate any safety issues that arise during the conduct of the study. Treatment allocation of randomized patients will remain blinded throughout the study course until the last patient completes 12 months of follow-up.

Finally, the Phase 2 CLI Study will not begin enrolling patients until after the first interim safety analysis in the Phase 2 IC study (60 patients with at least 4 weeks of follow up) has been conducted by the DMC and authorization has been granted to proceed with that study.

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