

Scientific Abstract

CLI is the most severe manifestation of PAD in the legs with both high societal and individual patient costs. Current therapeutic options are inadequate, particularly for patients who are not candidates for revascularization, or in whom revascularization has failed. Even in patients who undergo peripheral arterial intervention, there remains a great need to improve the clinical outcome of limb preservation. Therapeutic Angiogenesis is the ability to promote the growth of new blood vessels for the treatment of disorders of inadequate tissue perfusion. The HGF Plasmid has demonstrated potential for promoting angiogenesis in ischemic tissue based on in vitro, animal, and clinical models.

At present, approximately 8.5 million Americans have PAD which is either asymptomatic, claudication or critical leg ischemia. The potential benefit from HGF plasmid induced angiogenesis to improve the pathophysiology of CLI is highly dependent on the adequacy of small and medium sized vessels in distribution of blood to compromised tissues. Angiogenesis has the potential to address a significant unmet need in the treatment of CLI, a disease which has a substantial morbidity and mortality rate in the United States. Currently, there are limited therapeutic options such as revascularization, which is expensive and not always technically possible. The result of the high mortality and morbidity in CLI patients is a significantly reduced quality of life as well as high financial societal costs.

AnGes-MG, Inc. has begun investigating hepatocyte growth factor (HGF) as a potential therapy for patients with PAD. HGF has been shown to be involved in the proliferation, mobility, and morphogenesis of various cells. It is also considered to be a humeral mediator of epithelial-mesenchymal interactions during embryonic development and organogenesis. HGF has potent angiogenesis activity that may result from a combination of direct effects on endothelial cells and indirect effects, including paracrine up-regulation of VEGF on vascular smooth muscle cells. HGF shares many similarities to VEGF but lacks its ability to increase vascular permeability. Endothelial cells express the HGF-specific receptor, c-met, whose expression is up regulated in response to hypoxia. Thus, similar to VEGF, HGF stimulates the growth of endothelial cells without causing proliferation of smooth muscle cells. In addition, HGF has a typical signal sequence that allows it to be secreted from cells.

In the planned clinical studies to evaluate the safety and effectiveness of plasmid encoded HGF in patients with moderate to severe PAD, plasmid HGF will be administered intramuscularly. The intramuscular route offers several advantages over intra-arterial administration. The intramuscular route of administration is less invasive and has been well tolerated in other clinical studies evaluating patients with PAD. Data from these studies as well as earlier investigations have demonstrated that striated muscle can take up and express foreign genes

expressed from "naked" plasmid DNA. The administration of plasmid DNA also obviates the immunological concerns associated with adenoviral vectors that have been used in gene therapy. In addition, naked plasmid DNA remains in a non-replicative, unintegrated, circular form so there is less chance for insertional mutagenesis.

The safety and effectiveness of plasmid encoded HGF is being investigated in a phase 1/2 study in patients with PAD due to arteriosclerosis or Buerger's disease in Japan. Clinical data generated in this study will support further investigation of HGF as angiotherapy for patients with critical limb ischemia. An interim report for this trial will be provided in the IND and include data on the 6 stage 1 patients (dosed 2 mg's on days 0 and 28) and 6 to 8 stage 2 patients (up to 4 dosed at 2 mg's on days 0 and 28; and 4 dosed at 4 mg's on days 0 and 28). AnGes anticipates completion of this trial prior to the initiation of the AG-CLI-0202 trial in January 2002.

The proposed trial, AG-CLI-0202, is presented as a phase I/II double-blind, randomized, parallel-group, dose-response trial (n=110) to evaluate the optimal dose and dosing regimen for the HGF plasmid. The trial entitled, "A Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of HGF Plasmid for the Treatment of Critical Leg Ischemia", will provide an evaluation of two doses of HGF versus placebo, 0.4 mg and 4.0 mg, as well as three treatment regimens, two doses at days 0 and 28, three biweekly doses and five weekly doses. Additional safety measures will include patient assessment before each dose and ongoing safety evaluations of the data by a DSMB. The primary outcome measure will evaluate the angiogenic properties of the HGF plasmid by primarily measuring the increase in subcutaneous TcPO₂ levels. Secondary outcome measures will include a reduction in major amputation rates, ulcer healing, improved pain at rest, quality of life, and hemodynamic measurements.

The results of this trial will be to establish a base of clinical information that will allow AnGes to properly design a Phase III clinical program.