

## **AG-CLI-0205**

### **Scientific Abstract**

Critical leg ischemia (CLI) is the most severe manifestation of peripheral artery disease (PAD) in the legs with both high societal and individual patient costs. Approximately 8.5 million Americans have PAD which is either asymptomatic, claudication or critical leg ischemia. Current therapeutic options are inadequate, particularly for patients who are not candidates for revascularization, or in whom revascularization has failed. There remains a great need to improve the clinical outcome of limb preservation, even in patients who undergo peripheral arterial intervention.

Therapeutic angiogenesis is the ability to promote the growth of new blood vessels for the treatment of disorders of inadequate tissue perfusion. AnGes, Inc. is investigating hepatocyte growth factor (HGF) as a potential therapy for patients with CLI. The HGF Plasmid (also known as AMG0001) contains the cDNA for human hepatocyte growth factor and has demonstrated potential for promoting angiogenesis in ischemic tissue based on *in vitro*, animal, and clinical studies.

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, HGF stimulates the growth of endothelial cells without causing proliferation of smooth muscle cells.

The safety and effectiveness of HGF Plasmid is currently being investigated in a phase II, double-blind, randomized, placebo-controlled, dose-response study in more than 100 subjects with CLI: *A Phase I/II double-blind, randomized, placebo-controlled study to assess the safety and efficacy of AMG0001 to improve perfusion in critical leg ischemia* (AG-CLI-0202, #0207-546). Subjects receive eight intramuscular injections of AMG0001 (0.4 or 4.0 mg) and/or placebo in one leg on days 0, 14 and 28. All administrations will be completed by the end of June 2005.

Study AG-CLI-0205 (*A Phase II Double-Blind, Randomized, Placebo-controlled Study to Assess the Safety and Efficacy of AMG0001 to Improve Perfusion in Critical Leg Ischemia in Subjects who have Peripheral Ischemic Ulcers*), is an extension of AG-CLI-0202. Subjects also receive eight intramuscular injections of AMG0001 or placebo in one leg on days 0, 14, and 28.

The significant differences between AG-CLI-0205, compared to AG-CLI-0202, are: (1) 15 subjects will receive 4.0 mg of AMG0001 and 5 subjects will receive placebo, (2) each of the eight injections will contain 3 ml (instead of 2 ml) of solution, (3) eligible subjects must have a peripheral ischemic ulcer, (4) duplex scanning will be used during the injection procedure to help identify the injection sites, (5) TcPO<sub>2</sub> measurements will not be performed, (6) an SF-36 evaluation will not be used. Also, the precise anatomical locations of injections for each subject

will be pre-determined by a central reader based on the screening angiogram. The effectiveness and feasibility of this method will be evaluated in order to design a phase III study.

The objectives of this study are to determine if AMG0001 intramuscular leg injections are safe and induce angiogenesis as determined by improved wound healing, reduction in amputation, improved pain at rest and improved hemodynamic measurements. The endpoints include improved wound healing at 3 months following the first treatment, reduction in the proportion of subjects who undergo a major amputation within 6 months following the first treatment, and improved pain at rest and hemodynamic measurements

The results of this study will provide insight into the response to AMG0001 treatment, possible mechanisms of action, and information useful in designing a phase III study.