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Scientific Abstract

Peripheral arterial disease (PAD) is a common disorder usually caused by atherosclerotic changes in the arteries supplying the lower extremities, resulting in ischemic limb disease. Clinical manifestations of lower extremity PAD are related to the severity of muscular ischemia, which depends on the degree of arterial stenosis. Intermittent claudication is a common, initial presentation. Critical limb ischemia denotes a condition of severe arterial obstruction due to advanced PAD, associated with breakdown of the skin or pain in the lower limb at rest. The natural history of critical limb ischemia has been well documented to have an inexorable downhill course, frequently leading to the amputation of the affected limb. Two main etiologies of PAD are known as atherosclerotic peripheral arterial disease and thromboangiitis obliterans (Buerger's disease).

Bypass surgery can be recommended for subjects with critical leg ischemia if the arterial circulation of the lower calf or foot includes a reconstituted artery, the outcomes of surgery involving small-size arteries are often unsatisfactory due to a high failure rate. Many subjects face amputation of their limb as the sole therapeutic option for the severe symptoms of critical limb ischemia, when percutaneous transluminal angioplasty (PTA) or bypass surgery fails to improve the symptoms. Psychological testing of such subjects typically shows quality-of-life indices similar to those of subjects with terminal cancer. It is estimated that about 150,000 subjects per year require lower-limb amputations for ischemic diseases in the United States alone. Their prognosis after amputation is even worse. The perioperative mortality for below-knee amputation is 5 to 10 percent and for above-knee amputation 15 to 20%. Moreover, full mobility is achieved in only 50% of below-knee and 25% of above-knee amputees. These forbidding statistics result from the lack of efficacious drug therapy for PAD. Consequently, there is an urgent need for novel treatment strategies for subjects with critical limb ischemia.

VM202, a DNA plasmid that expresses human hepatocyte growth factor (HGF), has demonstrated potential for stimulating angiogenesis in peripheral blood vessels in animal models. A similar plasmid, VMDA-3601, with the same DNA backbone, pCK, as VM202, and containing the therapeutic gene expressing vascular endothelial growth factor (VEGF165) protein, has been studied for the indication of PAD in Korea and is currently under phase II investigation sponsored by ViroMed Co. Ltd. The drug was well-tolerated and an increase in the number of vessels and pain reduction were observed in 7 out of 9 subjects dosed in the VMDA-3601 phase I trial.

This proposed trial entitled, "A Phase I, Dose-Escalation, Single Center Study to Assess the Safety and Tolerability of VM202 in Subjects with Critical Limb Ischemia" will be performed to evaluate safety, tolerability and preliminary efficacy of VM202. The study (n=12) will consist of four (4) cohorts with a total of 3 subjects enrolled in each cohort. For each dose cohort, VM202 will be administered as a local intramuscular injection in 2 divided doses with a 2 week interval between the injections. Preliminary efficacy (hemodynamic assessments), safety and tolerability will be evaluated at baseline (screening) and at designated time points after administration of VM202. All subjects will be followed for one year from the time of the first study drug administration. If a dose limiting toxicity is observed at any dose group, three additional subjects will be added to all dose groups and all evaluations will be repeated for these additional subjects.

ViroMed will use the results of the trial to design a phase II clinical study.