

NON-TECHNICAL ABSTRACT

SB-509-0701: A Phase 2 Repeat Dosing Clinical Trial of SB-509 in Subjects with Moderate to Severe Diabetic Neuropathy and Unmeasurable Nerve Conduction Velocity

Individuals with diabetes often experience tingling and numbness in their hands and feet. This condition is called diabetic neuropathy. Due to the numbness associated with diabetic neuropathy, individuals are often unable to detect injury. Thus, repeated injury can lead to ulcers and other wounds. In the worst-case scenario, the affected limb must be amputated. Although there are palliative treatments available for pain, burning, and tingling, there is no cure for diabetic neuropathy.

A protein growth factor called Vascular Endothelial Growth Factor-A (VEGF-A) is responsible for the growth and development of blood vessels and, like many protein hormones, has multiple roles in the body. In addition to its much-studied effects on blood vessel growth, VEGF-A has been shown to have a protective effect on nerves, suggesting the possibility that VEGF-A treatment might have a positive effect on diabetic neuropathy symptoms and the progression of the condition.

Several lines of evidence support the concept that VEGF-A may be useful for the treatment of diabetic neuropathy. First is the neuroprotective effects mentioned above; second is the observation that VEGF-A gene therapy reverses diabetic neuropathy in animals with diabetes; and finally, a Phase 1 clinical trial using VEGF-A gene therapy for subjects with neuropathy showed promising trends. A larger clinical trial is currently underway.

These experiments and clinical trials all use gene transfer methods. A piece of DNA that encodes for expression of VEGF-A is injected into the muscles of the affected limb. The cells of the muscle take up the DNA and begin producing VEGF-A protein. Sangamo BioSciences, Inc. has developed an alternative approach, based on animal studies that may be promising as a therapeutic.

Sangamo has developed a plasmid DNA (SB-509) that works by activating the endogenous VEGF-A gene. This is accomplished by providing a molecular switch, called a transcription factor, which binds to the VEGF-A DNA and switches on the gene, thus activating all isoforms of VEGF-A. This approach in practice is as simple as the conventional gene therapy methods currently being tested, but it may prove more effective because all three major forms of VEGF-A will be produced instead of just one.

This plasmid DNA has been tested in a Phase 1 trial in subjects with Diabetic Neuropathy. In the Phase 1 study 24 subjects were treated at the dose levels of 1, 5, 30 and 60 mg. Treatment was well-tolerated and there were no dose-limiting toxicities or drug-related serious adverse events. There were ten treatment-related adverse events, nine were in subjects treated with SB-509 and one in a subject treated with placebo. All AE's were reversible. The proposed Phase 2 repeat dosing clinical trial will use SB-509 in subjects with moderate to severe Diabetic Neuropathy and unmeasurable nerve conduction velocity. The objectives of the Phase 2 trial is to test whether repeat treatments of SB-509 will improve symptoms of diabetic neuropathy and improve nerve health as measured on neurologic examination and the speed of nerve conduction in the lower legs.