



VIPRINEX™

Derived from the venom of the Malayan pit viper, Viprinex™ is a thrombin-like enzyme that is highly specific to fibrinogen. When administered systemically, Viprinex™ has been shown to rapidly deplete plasma fibrinogen (it is a defibrinogenating agent). The effects are anticoagulation, improved blood viscosity and a secondary fibrinolytic or clot lysing action. Combined, these effects constitute a perfusion strategy that appears to restore and enhance blood flow to the affected area of the brain.

VIPRINEX™ PROFILE

Viprinex™ (ancrod) has been studied in nearly 2,000 acute stroke patients in various clinical studies in the U.S. and Europe and has the potential to double the available treatment window following the onset of stroke symptoms. Currently, the only available therapy for stroke must be administered within the initial three hours, significantly limiting the number of patients that may be treated.

One of the primary goals for the treatment of acute ischemic stroke is improving blood flow through a blocked vessel so that the flow of oxygen and nutrient supply to brain tissue is not interrupted or compromised. Brain tissue deprived of blood flow beyond a critical time point will die, resulting in permanent loss of neurological functions like speech and mobility. Fibrinogen, a protein involved in blood clotting, has been known to contribute to high blood viscosity, which in turn may impede blood flow to critical regions of the brain.

Thus, an agent that reduces fibrinogen levels may significantly impact stroke treatment. Through its combined actions

of indirect fibrinolysis, anticoagulation, and improved blood viscosity, we believe that Viprinex™ is uniquely capable of lysing blood clots, preventing new clot formation, and improving blood flow.

A randomized, double-blind, placebo-controlled U.S. Phase III clinical study was completed in 1998 to evaluate the safety and efficacy of Viprinex™ given within three hours after the onset of acute, ischemic stroke in 500 patients. In this study, Viprinex™ was shown to be effective in preserving functions of daily activities in this patient population.

A separate randomized, double-blind, placebo-controlled Phase III study was completed in Europe in 2000, enrolling patients within six hours of onset of acute ischemic stroke. The trial was stopped after a planned interim analysis indicated lack of efficacy. We believe that the higher dosing levels in the European trial and the use of protocol criteria that permitted entry of patients at higher risk of hemorrhage contributed to the trial's failure.



Our review of the relative strength of the positive U.S. findings versus the European findings suggests the need for a revised Viprinex™ dosing strategy, which will be one objective of our Phase III study.

ABOUT STROKE

According to the American Stroke Association, every 45 seconds someone in the U.S. suffers a stroke and every three minutes someone dies of one. It is the nation's third leading cause of death after diseases of the heart and all forms of cancer and is the leading cause of serious, long-term disability.

A stroke occurs when a blood vessel that carries oxygen and nutrients to the brain is either blocked (ischemic) by a clot or ruptures (hemorrhagic). When the tissues are deprived of needed blood they begin to die, affecting various parts of the body and causing paralysis and problems with speech, vision and other neurological functions. Less than ten percent of stroke patients are considered suitable for current therapies, and less than five percent actually receive treatment. The estimated direct and indirect costs of stroke in the U.S. in 2004 are \$53.6 billion.

PRODUCT / INDICATION	DEVELOPMENT STATUS	PRIMARY BENEFIT SOUGHT
VIPRINEX™ Ischemic Stroke	Knoll successfully completed Phase II and Phase III trials in the U.S.; failed a Phase III trial in Europe. Nearly 2000 stroke patients studied to date. We are undertaking additional Phase III testing.	Minimize neurological damage and maximize functional outcome while limiting adverse effects (intracranial hemorrhage). A new brief, single administration dosing regimen expected to yield optimized safety and efficacy when compared to multiple-day dosing regimens employed in earlier studies.