

**A phase I safety study in patients with severe hemophilia B (factor IX deficiency) using adeno-associated viral (AAV) vector to deliver the gene for human factor IX to skeletal muscle.**

NON-TECHNICAL ABSTRACT

Hemophilia B is the bleeding diathesis caused by a deficiency of functional blood coagulation factor IX. Currently, hemophilia B is treated by giving intravenous injections of clotting factor concentrates to hemophilia patients when they are bleeding. A difficulty with this treatment approach is that the clotting factors last in the circulation for only 12-18 hours, while the disease is lifelong. The goal of a gene therapy approach is to treat the disease by transferring to the patient the gene that makes factor IX protein, so that the protein is made constantly in the patient's own cells. The goal of this proposed phase I study is to examine the safety of one gene therapy approach, injection of an adeno-associated viral vector expressing human factor IX (AAV-hFIX) into the muscles of the leg. In the proposed study, men with severe hemophilia B will be admitted to the Clinical Research Center of The Children's Hospital of Philadelphia, where they will undergo a series of intramuscular injections of the AAV vector that results in the production of human factor IX. The design of the trial is a dose escalation study, beginning with doses that are not expected to result in therapeutic levels of factor IX. This means that the first group will receive the lowest dose, and each subsequent group will receive a higher dose until a therapeutic dose is achieved or until unacceptable toxicity occurs. The injections will be given into the muscles of the thigh, at anywhere from 6 to 20 injection sites, depending on the dose of vector to be administered. Patients will be monitored in the hospital for at least 24 hours after injection, then discharged and followed closely as outpatients. Parameters to be monitored include plasma factor IX levels, presence of inhibitory antibodies or factor IX "inhibitors", and blood tests to look for evidence of toxicity in organs such as the liver, kidneys and muscle, and blood cell counts. In addition, patients will undergo muscle biopsy (a small piece of the injected muscle tissue will be removed) at 2, 6 and possibly 12 months after injection, to analyze the injected muscle for the presence of the vector DNA sequences, and production of the factor IX protein. Patients will be seen in follow-up in outpatient clinics at frequent intervals for the first 12 months, then every 6 months for the rest of their lives. Ongoing evaluation at a hemophilia center is a part of routine management of hemophilia.