**BACKGROUND**

- Hemophilia B (affects approximately 80,000 people worldwide) is an X-linked, recessive, congenital bleeding disorder which results from a deficiency or dysfunction of coagulation clotting factor IX (FIX) protein.

- Individuals with the severe or moderately severe FIX deficiency classically experience spontaneous or minimally trauma induced hemarthroses that can lead to disabling hemophilia arthropathy, and other sequelae.

- Prophylaxis FIX protein replacement therapy may significantly reduce bleeding events but, adherence to prophylactic intravenous (IV) factor infusion has not been universally adopted.

**RATIONAL**

- Adeno-associated viral (AAV) vector-mediated gene transfer is an attractive treatment option for severe hemophilia B. AAV vectors are attractive because they are non-pathogenic, have a large human genome capacity, and can be introduced with high efficiency of transduction.

- Preliminary published data in AAV-mediated FIX gene transfer in severe hemophilia B demonstrated sustained mean FIX activity of 5.1 ± 1.7% of normal in six subjects at 2 x 10^12 vg/kg dose level for a median of 3.5 years.

- No out of subjects at 2 x 10^12 vg/kg dose level had an AAV vector capsid immune response that was controlled with a short course of prednisolone. However, the mean FIX activity levels failed to protect some subjects from spontaneous bleeding and did not universally allow for discontinuation of prophylaxis.

**METHODS**

- Spark Therapeutics and Pfizer are developing an investigational gene transfer product (SPK-9001) for the potential treatment for hemophilia B.

- SPK-9001 is a recombinant AAV vector containing the following elements:
  - A novel bio-engineered AAV capsid (AAV-Spark100) with liver-specific tropism
  - A FIX expression cassette with a strong liver-specific promoter to drive expression of a high-specific activity gain-of-function FIX variant R338L (FIXa-Parka)3

- An Phase 2 dose-escalation study to evaluate safety, tolerability, and kinetics of SPK-9001

**RESULTS**

- As of July 12-2016, first 4 subjects have been followed for 12 to 31 weeks after a single IV infusion of SPK-9001 at a dose level of 5 x 10^12 vg/kg.

- No product- or procedure-related adverse events, including none related to FIX inhibitor, have been observed to date.

- No hepatic transaminase values >1.5 ULN have been observed.

- There was a low T-cell response to the vector capsid and no response to the transgene, as monitored by ELISPOT analysis.

- No subjects have required immune suppression due to elevated hepatic transaminases.

- As of July 12-2016, subjects 1, 2, 3, and 4 showed FIX activity levels of 28%, 42%, 21%, and 35% of normal, respectively.

- All 4 dosed subjects are free from FIX infusions.

**CONCLUSIONS**

- Follow-up of a single IV infusion with 5 x 10^11 vg/kg of SPK-9001, subjects achieved consistent increase in steady-state FIX activity levels to a mean of 31.8% ± 6.9% of normal 8-week post vector administration.

- Study subjects have discontinued factor replacement therapy without break through bleeding events.

- Based on natural history data, FIX activity levels >12% of normal are likely to allow individuals with hemophilia to be free from spontaneous bleeding.

- No immune suppression has been required.

- To our knowledge, a dose of 5 x 10^12 vg/kg of an AAV-mediated FIX at the lowest dose thus far administered to achieve FIX activity levels of >20% of normal, without a requirement for immune suppression.

- Observation is ongoing and the study is actively recruiting candidates.

**Current active sites**

- The Children’s Hospital of Philadelphia (Georgeal@childhealth.edu)
- The University of Pittsburgh (ragni@pitt.edu)
- The University of California Davis (giermasz@ucdavis.edu)
- Weill Cornell Medical Center (jamieson@med.cornell.edu)
- St. Michael’s Hospital (toronto@smh.ca)

**References**


**Clinical trials.gov identifier: NCT02484092.**