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Preliminary Results of a Phase 1/2 Trial of SPK-9001, a Hyperactive FIX Variant Delivered by a Novel Capsid, Demonstrate Consistent Therapeutic Factor IX Activity Levels at the Lowest Dose Cohort

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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[1]
- Individuals with the severe or moderately severe FIX deficiency classically experience spontaneous or minimally trauma induced hemathroses that can lead to disabling hemophilia arthropathy, and other sequelae[2]
- Prophylaxis FIX protein replacement therapy may significantly reduce bleeding events but, adherence to prophylactic intravenous (IV) factor infusion has not been universally adopted due to the burden of 1-3X weekly IV infusions. Further, bleeding may occur at times FIX activity troughs[3]

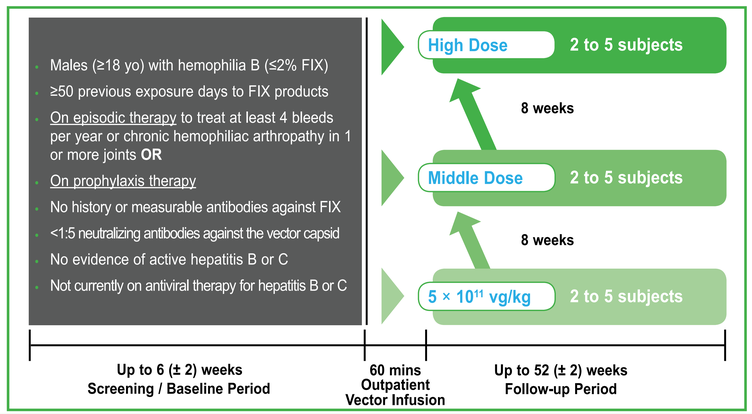
RATIONALE

- Adeno-associated viral (AAV) vector-mediated gene transfer for hemophilia B, a possible curable treatment, has demonstrated both safety and long-term expression of FIX[4]
- Previously published data in AAV-mediated FIX gene transfer in severe hemophilia B individuals demonstrated sustained mean FIX activity levels 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[5]
- 4 out of 6 subjects at 2 x 10^{12} vg/kg dose level had an AAV 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[5]

METHODS

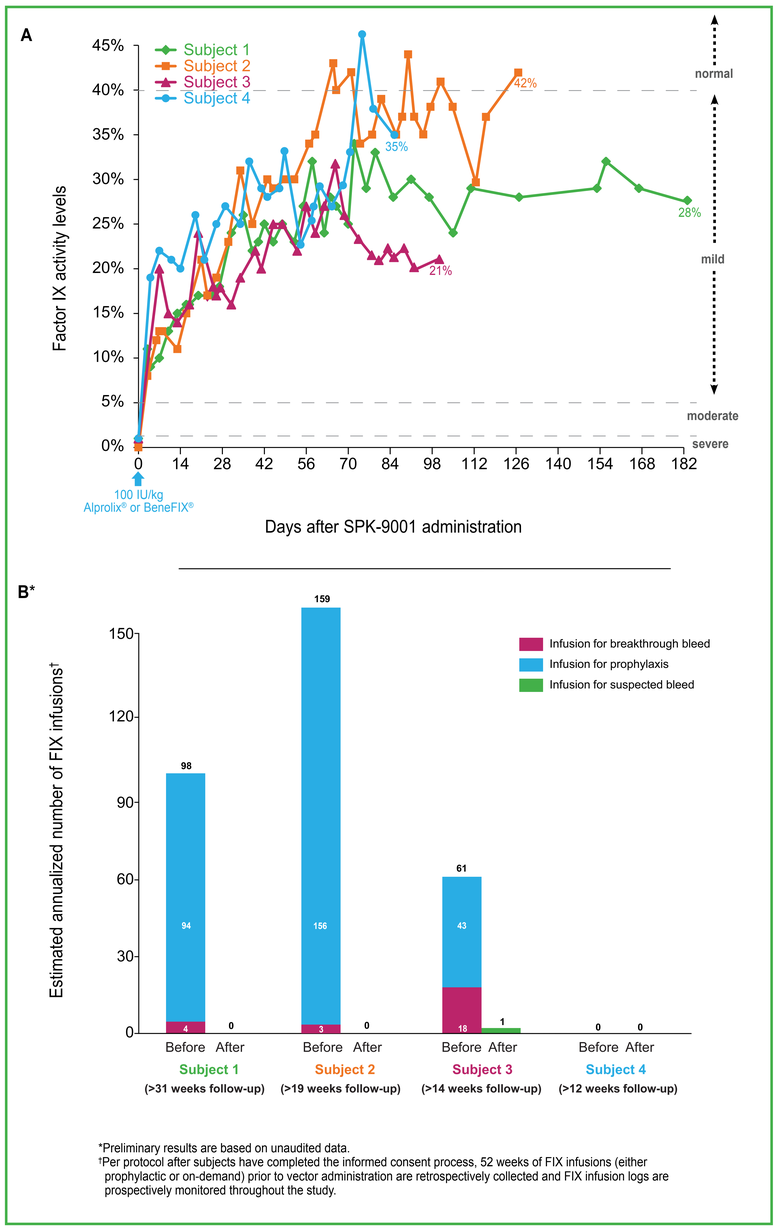
- Spark Therapeutics and Pfizer are developing an investigational gene transfer product (SPK-9001) for the potential treatment for hemophilia B
- SPK-9001 is a recombinant AAV vector containing the following elements:
  - A novel bio-engineered rAAV capsid (AAV-Spark100) with liver-specific tropism[6]
  - A FIX expression cassette with a strong liver-specific promoter to drive expression of a high- specific activity gain-of-function FIX variant R338L (hFIX-Padua)[6,7]
- An Phase 1/2 dose-escalation study to evaluate safety, tolerability, and kinetics of SPK-9001

Figure 1. SPK-9001-101 Proposed Study Design[8]



RESULTS

Figure 2. A single infusion with 5 x 10^{11} vg/kg of SPK-9001 resulted in an increase in FIX activity levels and a reduction of factor IX infusions



*Preliminary results are based on unaudited data.
†Per protocol after subjects have completed the informed consent process, 52 weeks of FIX infusions (either prophylactic or on-demand) prior to vector administration are retrospectively collected and FIX infusion logs are prospectively monitored throughout the study.

- 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^{11} vg/kg
- No product- and/or procedure-related adverse events, including none related to FIX inhibitor, have been observed to date
- No hepatic transaminase values >1.5 ULN have occurred
- 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. Subject 3 was treated for a suspected ankle bleed 2 days after vector administration; otherwise, no subjects have experienced any spontaneous or traumatic bleeding events

CONCLUSIONS

- Following 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 (±SD) 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[9]
- No immune suppression has been required
- To our knowledge, a dose of 5 x 10^{11} vg/kg of an AAV-mediated FIX is 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 (GeorgeL@email.chop.edu)
  - The University of Pittsburgh (ragni@pitt.edu)
  - The University of Mississippi Medical Center (lmsullivan@umc.edu)
  - The University of California Davis (giermasz@ucdavis.edu)
  - Weill Cornell Medical Center (cam9061@med.cornell.edu)
  - St. Michael's Hospital Toronto (TeitelJ@smh.ca)
- Clinicaltrials.gov identifier[8]: *NCT-02484092*

- **32nd International Congress of the World Federation Hemophilia presentations:**
  - **July 25, 2016 16:00 - 16:10 EDT moderated-poster oral presentation.** Preliminary results of a Phase 1/2 trial of SPK-9001, a hyperactive FIX variant delivered by a novel capsid, demonstrate consistent FIX activity levels at the lowest dose cohort by Dr. Lindsey George from The Children's Hospital of Philadelphia
  - **July 26, 2016 12:40 - 13:00 EDT Pfizer satellite symposium oral presentation.** Toward endogenous prophylaxis: Update on gene therapy by Dr. S. Sullivan from Mississippi Center for Advanced Medicine
  - **July 27, 2016 14:15 - 14:45 EDT Late-breaking - gene therapy oral presentatin.** SPK-9001 adeno-associated virus mediated gene therapy for Hemophilia B: sustained factor IX expression at therapeutic levels without immunosuppression by Dr. Lindsey George from The Children's Hospital of Philadelphia

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