A Phase I/II multicenter gene therapy clinical study for Fabry Disease

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FABRY DISEASE

- Fabry disease is an X-linked lysosomal storage disease caused by mutations in the GLA gene, which encodes the lysosomal enzyme alpha-galactosidase A (α-Gal A).
- Lack of α-Gal A activity results in the progressive, systemic accumulation of its primary substrate, globotriaosylceramide (Gb3), and its deacetylated sialic acid form, globotriaosylsphingosine (lyso-Gb3).
- Long-term accumulation of these substrates leads to renal, cardiac, and/or cerebrovascular disease, with reduced life expectancy.
- Depending on the GLA mutation and residual α-Gal A enzyme level, the disease presents as classic early-onset Fabry disease or as an attenuated phenotypic form later in life.
- Patients with amenable mutations may be managed with oral chaperone therapy.

STUDY DESIGN

- For this open-label, first-in-human clinical trial with ST-920, a recombinant adeno-associated virus (AAV2/6) vector containing the human GLA GNA which encodes for the enzyme α-Gal A.
- The purpose of this study is to evaluate the safety and tolerability of ascending doses of ST-920.
- The constant production of α-Gal A in humans should lead to reduction and potential clearance of Fabry disease substrate Gb3 and lysoGb3 from target organs.
- The same AAV vector with liver-targeted gene delivery has been administered previously in a single gene therapy infusion resulted in supraphysiological expression of plasma α-Gal A activity, reaching stable levels by day 14.
- Gb3/lysoGb3 levels in plasma, liver, and other tissues reached near-normal levels by 3 months after administration.
- A potentially improved pharmacokinetic profile of gene therapy could also result in improved cross-correction via mannose-mediated uptake (cross-correction) and reduced production of antibodies against the enzyme, as has been demonstrated in mouse models of Fabry and Pompe disease.1,2

RATIONAL FOR GENE THERAPY IN FABRY DISEASE

- Unmet medical need with current standard of care including ERT:
  - Short half-life necessitates a lifetime of infusions every other week.
  - A lack of α-Gal A activity results in the progressive, systemic accumulation of its primary substrate, globotriaosylceramide (Gb3), and its deacetylated sialic acid form, globotriaosylsphingosine (lyso-Gb3).
  - Long-term accumulation of these substrates leads to renal, cardiac, and/or cerebrovascular disease, with reduced life expectancy.
- The purpose of this study is to evaluate the safety and tolerability of ascending doses of ST-920.
- Patients with amenable mutations may be managed with oral chaperone therapy.

ENDPOINTS

- Primary endpoint: Incidence of treatment-emergent adverse events
- Additional safety evaluations will include the following:
  - Renal function, laboratory chemistry, and liver tests, vital signs, electrocardiogram, and echocardiogram.
  - Serial α-Gal A enzyme and urinary Gb3 levels.
  - Frequency of ERT infusion
  - ERT treatment response
  - Cardiac function and left ventricular mass, measured by cardiac MRI
  - Estimateglomerular filtration rate (eGFR) 5 mL/min/1.73 m²
  - New York Heart Association Class III or higher
  - Contradication to death
  - Active viral infection
  - Currently receiving dialgastat

INVESTIGATIONAL SITES

**Site/Principal Investigator**

- 1. The Icahn School of Medicine at Mount Sinai, New York, NY, USA; Bernard Souberbielle, MD, PhD
- 2. University of Cincinnati College of Medicine, Cincinnati, OH, USA; John Bernat, MD
- 3. University of Iowa, Iowa City, IA, USA; Robert Hopkins, MD
- 4. University of Washington Medical Center, Seattle, WA, USA; Dr. Goker Alpan, MD
- 5. New York University, New York, NY, USA; Lea Leavitt AD, Konkle BA, Stine K, et al.
- 6. Sangamo Therapeutics, Inc., CA, USA; Dr Hughes

STUDY STATUS

- Two patients were dosed in cohort 1. Two patients have been dosed in cohort 2, and one patient has been dosed in cohort 3.

REFERENCES


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- This study is sponsored by Sangamo Therapeutics.

DISCLOSURES

BMC and CP are employees of Sangamo Therapeutics. ISR and SI were employees of Sangamo Therapeutics at the time of the study.