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

Poster #78

Jaya Ganesh, MD,[1] Ozlem Goker-Alpan, MD,[2] Sravan Jaggumantri,[3] Bernard Souberbielle, MD,[3] Bettina Cockroft, MD[3]

[1]The Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Lysosomal and Rare Disorders Research and Treatment Center, Fairfax, VA, USA; [3]Sangamo Therapeutics, Inc., Brisbane, CA, USA

Fabry disease

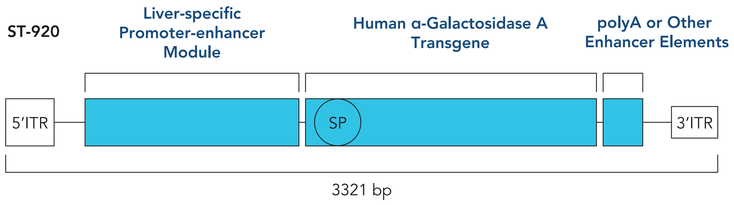
- Fabry disease is an X-linked lysosomal storage disease caused by mutations in the *GLA* gene, which encodes the lysosomal enzyme alpha-galactosidase A (α-Gal A)
- Lack of α-Gal A activity results in the progressive, systemic accumulation of its primary substrate, globotriaosylceramide (Gb3) and its deacetylated soluble 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 either classical early-onset Fabry disease in childhood/adolescence or as an attenuated (adult) form later in life
- In both classical and adult forms, the current standard of care is enzyme replacement therapy (ERT) using recombinant α-Gal A. Infusion of recombinant α-Gal A into the bloodstream allows transfer to secondary tissues via mannose-6-phosphate receptor-mediated uptake (cross-correction)
- Treatment with ERT necessitates a lifetime of biweekly infusions. In addition, a significant percentage of patients eventually generate antibodies to the recombinant enzyme, which may impact the activity of the infused recombinant α-Gal A

Rationale for gene therapy in Fabry disease

- Unmet medical need with current standard of care with ERT:
  - Short half-life necessitates lifetime infusions, with associated risk of infusion-related reactions
  - A significant percentage of patients eventually generate antibodies to the recombinant enzyme
  - A considerable number of patients develop disease manifestations despite treatment[1]
- Gene therapy administered as a single infusion to patients with classical Fabry disease using a liver-tropic viral vector provides the *GLA* gene that encodes the enzyme α-Gal A, allowing a constant and long-term production of the missing enzyme
- Once produced by the liver cells, the enzyme is transported by the bloodstream to cells through cross-correction. Nonclinical studies show that supraphysiological constant levels of the enzyme in the blood are needed in order to promote clearance of the substrate in the target organs (e.g., kidney and heart)[2]
- Another potential benefit is the different pharmacokinetic profile of gene therapy promoting better cross-correction, which may also lead to immune tolerance (and therefore minimize the production of antibodies against the enzyme) as demonstrated in mouse models of Fabry disease and in Pompe disease

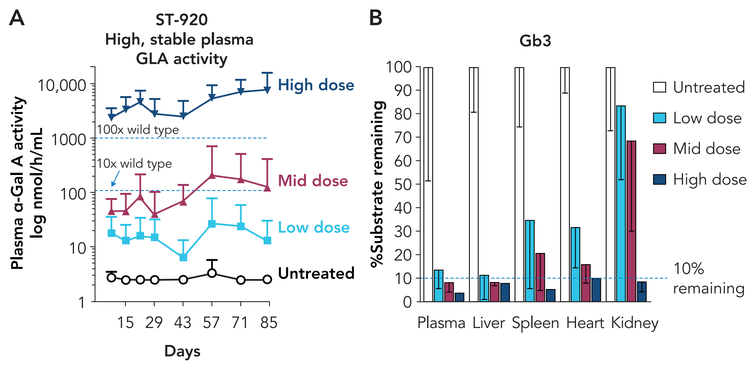
ST-920 and the STAAR study

- This is the first-in-human treatment with ST-920, a recombinant adeno-associated virus (rAAV) 2/6 vector encoding the cDNA of human α-Gal A, which has a sequence identical to the wild type enzyme
- 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 enable reduction and potentially clearance of Fabry disease substrates Gb3 and lyso-Gb3 from target organs
- The same rAAV capsid liver-targeted gene therapy has been previously administered in patients with hemophilia A (SB-525), exhibiting a positive benefit:risk profile[3]



ST-920 preclinical data

- Experiments in GLAKO (*GLA* knockout) mice showed that administration of a single ST-920 dose resulted in supraphysiological expression of plasma α-Gal A activity, reaching stable levels by day 14 (**A**)[4]
- Gb3/lyso-Gb3 levels in plasma, liver, and other tissues reached near normal levels by 3 months post administration (**B**). Appropriate glycosylation of the α-Gal A enzyme produced from liver cells was confirmed by in vitro experiments to ensure efficient mannose-6-phosphate mediated lysosomal uptake and cross-correction in target tissues



Study design

- **STAAR (ST-920-201) is a Phase I/II, dose-ranging, single-dose, open-label, multicenter study to assess the safety and tolerability of ST-920 in adult patients (>18 years of age) with classical Fabry disease**
- On day 1, patients are infused intravenously with a single dose of ST-920 and followed for a period of 52 weeks. Patients will then be followed in a separate long-term follow-up study for a total of at least 5 years from ST-920 infusion. At least 2 patients will be dosed in each dose cohort with a potential expansion in each cohort
- The study has safety oversight by an independent safety monitoring committee
- Patients who are on stable ERT can discontinue ERT after ST-920 dosing in a controlled and monitored fashion, at the discretion of the patient and the investigator
- After dose escalation, the study will be expanded to include female patients, as well as patients with Fabry-associated cardiac and renal disease

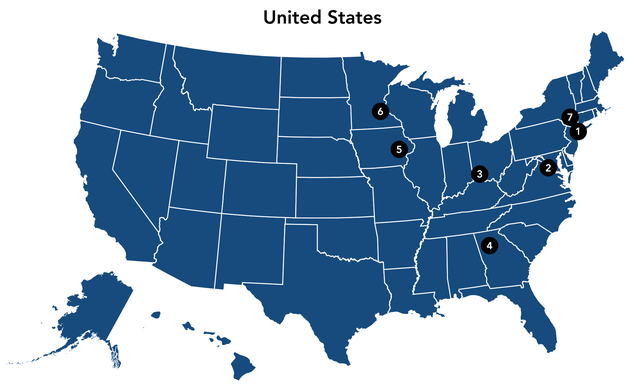
Key inclusion/exclusion criteria

- **Key inclusion criteria:**
  - Classical Fabry disease
  - Male patients ≥18 years of age
  - Patients who are on ERT; or are ERT-naïve; or are ERT-pseudo-naïve
- **Key exclusion criteria:**
  - Neutralizing activity to AAV6 capsid
  - Known to be unresponsive to ERT or showing recent or continued hypersensitivity response to ERT
  - History of liver disease and liver dysfunction
  - Estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2
  - New York Heart Association Class III or higher
  - Contraindication to steroids
  - Active viral infections
  - Currently receiving migalastat

Endpoints

- **Primary endpoint:**
  - Incidence of treatment-emergent adverse events
- **Additional safety evaluations will include:**
  - Routine hematology, chemistry, and liver tests; vital signs; electrocardiogram; and echocardiogram
  - Serial alpha fetoprotein testing and magnetic resonance imaging (MRI) of liver to monitor for liver mass
- **Secondary endpoints:**
  - Change from baseline at specific time points over the 1-year study period in:
    - α-Gal A activity, Gb3 and lyso-Gb3 levels in plasma
    - Frequency of ERT infusion
    - eGFR calculated using the CKD-EPI formula
  - ST-920 vector clearance
- **Exploratory endpoints:**
  - Change from baseline at specific time points over the 1-year study period in:
    - Left ventricular mass index measured by cardiac MRI
    - Quality of life, Fabry disease severity, neuropathic pain, gastric symptoms
  - Immune response to AAV6 capsid and α-Gal A

Investigational sites



Site/Principal Investigator

1. The Icahn School of Medicine at Mount Sinai, New York - **Dr Ganesh**
2. Lysosomal and Rare Disorders Research and Treatment Center (LDRTC), Fairfax, Virginia - **Dr Goker-Alpan**
3. Cincinnati Children's Hospital Medical Center - **Dr Hopkin**
4. Emory University School of Medicine, Atlanta - **Dr Wilcox**
5. University of Iowa Hospital and Clinics, Iowa City - **Dr Bernat**
6. University of Minnesota Medical Center, Minneapolis - **Dr Whitley**
7. NYU Langone Health Neurogenetics, New York - **Dr Lau**

Study status

- Two patients were dosed in Cohort 1. Enrollment has initiated for Cohort 2

References

1. Del Pino M, Andrés A, Bernabéu AÁ, et al. Fabry nephropathy: an evidence-based narrative review. *Kidney Blood Press Res.* 2018;43(2):406-421.
2. Huston MW, Yasuda M, Pagant S, et al. Liver-targeted AAV gene therapy vectors produced by a clinical scale manufacturing process result in high, continuous therapeutic levels of enzyme activity and effective substrate reduction in mouse model of Fabry disease. *Mol Genet Metab.* 2019;126(2):S77.
3. Leavitt AD, Konkle BA, Stine K, et al. Updated follow-up of the Alta study, a phase 1/2 study of giroctocogene fitelparvovec (SB-525) gene therapy in adults with severe hemophilia A. Presented virtually at: 62nd ASH Annual Meeting and Exposition; December 5-8, 2020.
4. Yasuda M, Huston MW, Pagant S, et al. AAV2/6 gene therapy in a murine model of Fabry disease results in supraphysiological enzyme activity and effective substrate reduction. *Mol Ther Methods Clin Dev.* 2020;18:607-619.

Acknowledgments

- We would like to thank the Fabry patients who have graciously agreed to screen and participate in this clinical trial. We would also like to thank the clinical sites, Principal Investigators, and coordinating staff for their participation in the STAAR clinical trial and their hard work initiating this study, as well as the Sangamo Bioanalytical Development and Clinical Development teams
- This study is sponsored by Sangamo Therapeutics, Inc.

Disclosures

- SJ, BS, and BC are employees of Sangamo Therapeutics, Inc.

Presented at: 17th Annual WORLD Symposium; February 8–12, 2021