PO19-2517

Preliminary results of STAAR, a Phase I/II study of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease and long-term follow-up

Jaya Ganesh,[1] Patrick Deegan,[2] Ozlem Goker-Alpan,[3] Robert J. Hopkin,[4,5] John A. Bernat,[6] William Wilcox,[7] Liching Cao,[8] Michael Chen,[8] Lisa H. Shiue,[8] Emma Bowden,[8] Sravan Jaggumantri,[8] Cristobal Passalacqua,[8] Bernard Souberbielle,[8] Bettina M. Cockroft[8]

[1]The Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]Addenbrooke's Hospital, Cambridge, UK, [3]Lysosomal and Rare Disorders Research and Treatment Center, Fairfax, VA, USA, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [5]University of Cincinnati College of Medicine, Cincinnati, OH, USA, [6]University of Iowa, Iowa City, IA, USA, [7]Emory University School of Medicine, Atlanta, GA, USA, [8]Sangamo Therapeutics, Inc., Brisbane, CA, USA

Introduction

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)
- The current standard of care for most patients is intravenous enzyme replacement therapy (ERT); patients with amenable mutations may alternatively be managed with oral chaperone therapy
- Patients who receive ERT require lifelong infusions every other week
- Despite treatment, patients may still experience disease progression and organ damage
- Efficacy of ERT in preventing irreversible cardiac and renal disease has been shown to be lower in advanced cases compared to early treatment[1]

Isaralgagene Civaparvovec (ST-920), the STAAR Study and Long-term Follow-up

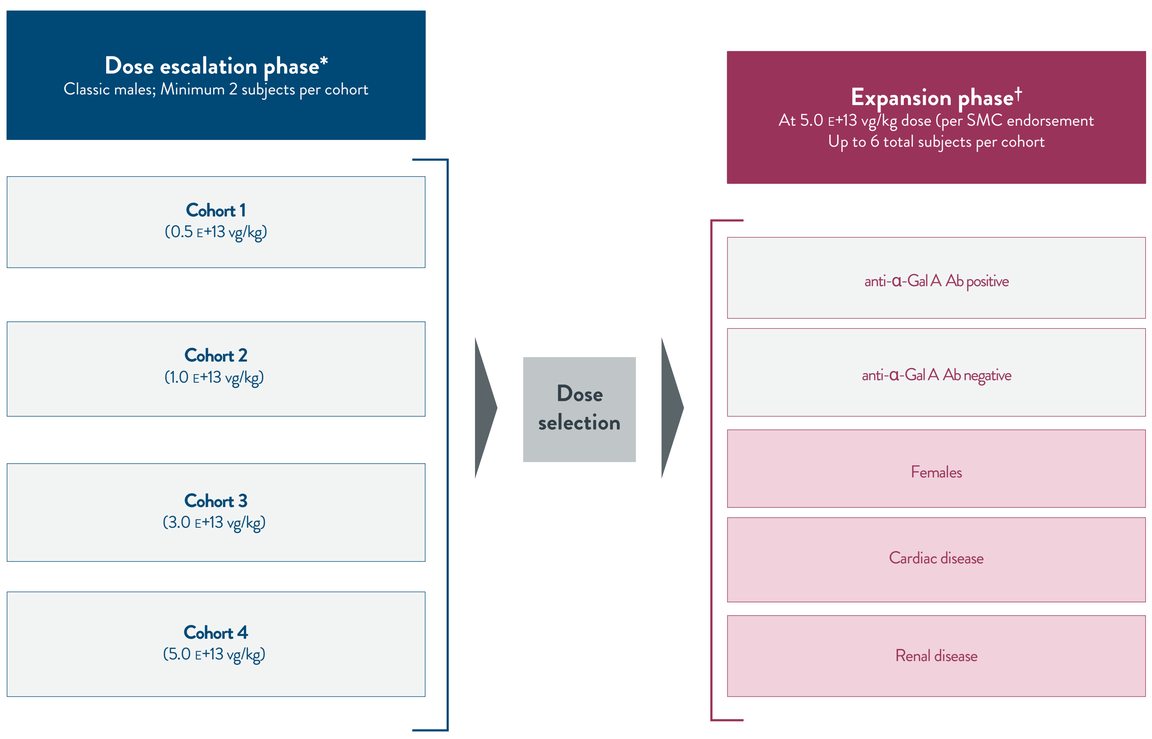
- STAAR is an ongoing, first-in-human clinical study with ST-920, a recombinant adeno-associated virus (rAAV2/6) vector containing the human *GLA* cDNA that encodes for the enzyme α-Gal A
- The functional gene is delivered to the liver; hepatocytes synthesize α-Gal A, which is released into the bloodstream
- The constant production of α-Gal A should lead to a reduction and potentially the clearance of Fabry disease substrates such as globotriaosylsphingosine (lyso-Gb3) from target organs
- The same rAAV vector with liver-targeted gene delivery has been administered previously in subjects with hemophilia A (giroctocogene fitelparvovec), exhibiting a positive risk–benefit profile[2]
- The purpose of this study is to evaluate the safety, tolerability, and efficacy of ascending doses of ST-920

Methods

Study Design

- STAAR (ST-920-201) is a phase 1/2 dose-ranging, single-dose, open-label, multicenter study to assess the safety and tolerability of ST-920 in adults (≥18 years old) with Fabry disease (NCT04046224) (**Figure 1**)
- On day 1, subjects are infused intravenously with a single dose of ST-920 and followed up for 52 weeks. Subsequently, subjects are enrolled in the long-term follow-up (LTFU) study (NCT05039866)
- During the dose escalation phase, at least 2 subjects (either antibody positive or negative to α-Gal A) are dosed in each dose cohort
- The dose escalation phase includes men with classic Fabry disease; the subsequent expansion phase also includes women, as well as subjects with Fabry-associated cardiac and renal disease
- Subjects who are on stable ERT may withdraw from ERT after ST-920 dosing in a controlled and monitored fashion at the discretion of the subject and the investigator

Figure 1. Phase 1/2 STAAR Study Design



*Safety and efficacy data of each cohort was reviewed by a safety monitoring committee (SMC) prior to dose escalation.
†The dose for the expansion cohorts may be reassessed if there are emerging safety considerations.
α-Gal A, alpha galactosidase A; Ab, antibody; vg/kg, vector genomes per kilogram of body weight.

Eligibility Criteria

Inclusion criteria:

- ≥18 years of age with Fabry disease
- On a stable ERT regimen, or ERT-naïve, or ERT-pseudo-naïve (no ERT treatment in the prior 6 months)

Key Exclusion Criteria

- Neutralizing activity to AAV6 capsid
- Judged to be unresponsive to ERT, or showing recent or continued hypersensitivity response to ERT
- History of clinically significant liver disease or liver dysfunction
- Estimated glomerular filtration rate (eGFR) ≤40 mL/min/1.73 m^2
- New York Heart Association Class III heart failure or higher
- Contraindication to steroids
- Active infection with hepatitis A virus, active or occult hepatitis B virus infection, active infection with hepatitis C virus (RNA positive), infection with the human immunodeficiency virus, or active or latent infection with tuberculosis
- Currently receiving migalastat

Endpoints

Primary endpoint:

- Incidence of treatment-emergent adverse events (AEs)

Additional safety evaluations will include the following:

- 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 potential formation of any 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
  - Cardiac function and left ventricular mass, measured by cardiac MRI (cMRI)
- rAAV2/6 vector clearance

Key exploratory endpoints:

- Quality of life, Fabry disease symptoms, and neuropathic pain scores
- Immune response to AAV6 capsid and α-Gal A

Results

Baseline Subject Characteristics

- Here we present preliminary data (cutoff February 14, 2022) from 3 ascending dose cohorts
- Six men with classic Fabry disease were dosed, with a mean age (SD) of 36.3 (10.4) years (**Table 1**)
  - Two subjects in Cohort 1 (0.5e13 vg/kg), 2 subjects in Cohort 2 (1.0e13 vg/kg), and 2 subjects in Cohort 3 (3.0e13 vg/kg)
- Both Cohort 1 participants completed the dose-finding study with 1 year of follow-up and are now enrolled in the LTFU study (follow-up for an additional 4 years)

Table 1. Baseline Subject Characteristics

	Cohort 1 (n=2) 0.5e13 vg/kg		Cohort 2 (n=2) 1.0e13 vg/kg		Cohort 3 (n=2) 3.0e13 vg/kg	
	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6
Age (years)	48	25	42	22	39	42
On ERT	Yes	No; pseudo-naïve	No; pseudo-naïve	Yes	Yes	Yes
Plasma α-Gal A activity (nmol/h/mL)*	1.54	0.92	Below LOQ	2.44	0.91	Below LOQ
Plasma lyso-Gb3 (ng/mL)*	22.1	18.1	83.2	11.1	32.9	1.91
Primary disease signs and symptoms	• Hypohidrosis • Tinnitus and vertigo • Left ventricular hypertrophy • Palpitations • Anemia • Leg edema	• Anhidrosis • Tinnitus • Acroparesthesia† • Sinus bradycardia • Left ventricular hypertrophy	• Hypohidrosis • Tinnitus and vertigo • Acroparesthesia† • ECG sinus arrhythmia	• Hypohidrosis • Neuropathic pain • Aortic root dilation	• Tinnitus • High-frequency hearing loss • Acroparesthesia† • Sinus bradycardia • Loose stool and constipation	• Hypohidrosis • Tinnitus • Neuropathic pain • Acroparesthesia†
Renal function (eGFR; mL/min/1.73 m^2)*‡	101.4	111.4	112.9	100	91.5	80
Pre-existing α-Gal A Abs	Positive	Negative	Positive	Positive	Positive	Negative
Mutation	G261D	T1411	W340R	S297Y	Q283X	D215S
Length of follow-up (weeks)	64 [52 + 12 (LTFU)]	64 [52 + 12 (LTFU)]	48	36	16	4

*The time point immediately preceding ST-920 administration was presented as the baseline value.
†Burning, tingling, or numbness in the extremities.
‡eGFR was calculated using the CKD-EPI.
α-Gal A, alpha galactosidase A; Ab, antibody; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; LOQ, limit of quantitation; LTFU, long-term follow-up; lyso-Gb3, globotriaosylsphingosine; vg/kg, vector genomes per kilogram of body weight.

Safety and Tolerability

- ST-920 continues to be generally well tolerated
- Eleven treatment-related AEs occurred in 3 subjects (**Table 2**); all were Grade 1 (mild)
  - No treatment-related serious AEs were reported
- There were no liver enzyme elevations requiring steroid treatment

Table 2. Treatment-Related Adverse Events

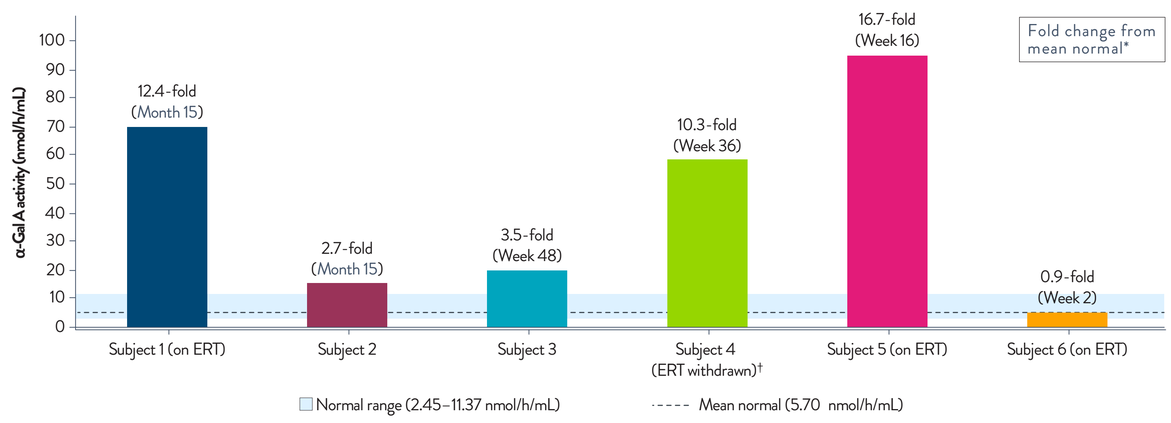
MedDRA Preferred Term	Cohort 1 (0.5e13 vg/kg) (n=2)		Cohort 2 (1.0e13 vg/kg) (n=2)		Cohort 3 (3.0e13 vg/kg) (n=2)		Overall (N=6)	
	n	Events	n	Events	n	Events	n	Events
Treatment-related adverse events (total)	**1**	**3**	**1**	**2**	**1**	**6**	**3**	**11**
Pyrexia	0	0	1	2	1	1	2	3
Hemoglobin decreased	1	1	0	0	0	0	1	1
Platelet count increased	1	1	0	0	0	0	1	1
Rash	1	1	0	0	0	0	1	1
Headache	0	0	0	0	1	1	1	1
Myalgia	0	0	0	0	1	1	1	1
Fatigue	0	0	0	0	1	1	1	1
Abdominal pain	0	0	0	0	1	1	1	1
Frequent bowel movements	0	0	0	0	1	1	1	1

MedDRA, Medical Dictionary for Regulatory Activities; vg/kg, vector genomes per kilogram of body weight.

Plasma α-Gal A Activity and Lyso-Gb3 Concentration

- Sustained, elevated α-Gal A activity was observed through the last sampling point for Subjects 1-5, including the 3 months of LTFU for Subjects 1 and 2 (**Figure 2**)
- α-Gal A activity had increased to within normal range at week 2 for Subject 6
- The first subject to be withdrawn from ERT, Subject 4, continues at 12 weeks to exhibit consistently and significantly elevated α-Gal A plasma activity, is clinically stable with moderate increase in lyso-Gb3 levels, and remains off ERT
- Subject 3 (pseudo-naïve) exhibited a higher elevation in plasma lyso-Gb3 pre-treatment, which showed approximately a 40% reduction within 10 weeks after dosing that was maintained through week 48
- Subjects 1 (on ERT), 2 (pseudo-naïve), 5 (on ERT), and 6 (on ERT) with lower baseline levels of plasma lyso-Gb3, maintained steady levels through the latest follow-up date

Figure 2. Plasma α-Gal A Activity at Cutoff



Biomarker results were evaluated from the 6 subjects in dose cohorts 1, 2, 3 (0.5e13 vg/kg, 1.0e13 vg/kg, 3.0e13 vg/kg) as of the cutoff date of February 14, 2022.
*Fold change was calculated at last measured time point. α-Gal A activity was measured using a 3-hour reaction time and is presented in nmol/h/mL. For Subjects 1, 4-6, sampling was at ERT trough. Normal range and mean were determined based on healthy male individuals.
†Subject was withdrawn from ERT at week 24.
α-Gal A, alpha galactosidase A; ERT, enzyme replacement therapy; LTFU, long-term follow-up.

Cardiac Evaluation

- Cardiac progression was evaluated by cMRI
  - For Subject 1, left ventricular hypertrophy was seen on cMRI, which increased during the study run-in phase and stabilized following 1 year of treatment
  - Subject 2 had mild biventricular dilation at baseline, which improved on cMRI at 1 year
  - Subjects 3 and 4 had normal cMRIs at baseline and 24 weeks
  - Subject 5 had mild left ventricular hypertrophy at baseline. Subject 6 had normal cMRI at baseline

Conclusions and Next Steps

- Up to the cutoff date of February 14, 2022, isaralgagene civaparvovec (ST-920) has been generally well tolerated, and no treatment-related AEs that were serious or higher than Grade 1 occurred
- None of the treated subjects exhibited elevations of transaminases requiring steroid treatment
- Elevated α-Gal A activity has been maintained in all subjects dosed with ST-920, extending from within normal reported range and up to 16.7-fold above mean normal, up to 15 months post infusion
- Subject 4 was withdrawn from ERT and remained clinically stable, with sustained elevated levels of α-Gal A 12 weeks post withdrawal
- Three subjects have anecdotally reported improvements in their symptoms, including improvements in the ability to sweat
- No progression of Fabry cardiomyopathy was observed in those subjects who presented with signs of cardiomyopathy on cardiac MRI at baseline
- STAAR is an ongoing study and based on these encouraging emerging data, phase 3 planning has been initiated
- Since the cutoff date, an additional 4 subjects (for a total of 10) have been dosed, including the first subject in the expansion phase. An additional 3 subjects have successfully been withdrawn from ERT.

References

1. Del Pino M, Andrés A, Bernabéu AÁ, et al. *Kidney Blood Press Res*. 2018;43(2):406-421.
2. Leavitt AD, Konkle BA, Stine K, et al. *Blood*. 2020;136(Suppl 1):12.

Acknowledgments

We would like to thank the patients who have graciously agreed to be screened 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 for their hard work initiating this study, as well as the Sangamo Biomarker and BioAnalytical Sciences and Clinical Development teams.
This study is sponsored by Sangamo Therapeutics.

Disclosures

JG: consultant, Amicus, Sangamo, Sanofi Genzyme, Takeda, Watermark Research Partners. OG-A: advisory boards and consultant for Amicus, Sanofi Genzyme, Takeda, Sangamo, 4DMT, Avrobio; research grants, Amicus, Freeline, Genentech, Protalix, Sangamo, Sanofi Genzyme, Takeda, Sangamo, 4DMT, Avrobio; speaker, Sanofi Genzyme, Takeda. RJH: advisory boards, Amicus Therapeutics; consultant, Amicus, Avrobio, Chiesi, Sanofi Genzyme; research grants, Amicus, Protalix, Sangamo, Sanofi Genzyme, Takeda; honoraria, Amicus, Avrobio, Chiesi, Protalix, Sanofi Genzyme; speaker, Amicus, Sanofi Genzyme. JB: advisory boards, Sanofi Genzyme, Takeda; research grants, Avrobio, BioMarin, Idorsia, Pfizer, Protalix, Sangamo, Sanofi Genzyme, Takeda. PD: advisory boards, Sanofi Genzyme, Takeda, Amicus; consultant, Sanofi Genzyme; honoraria, Sanofi Genzyme and Takeda. LC, MC, CP, LHS, EB, and BMC are employees of and hold ownership interest in Sangamo (less than 5%). BS and SJ were employees of Sangamo at the time of the study. CP and BS have received intellectual property rights/patents from Sangamo.

Presented at SSIEM 2022 in Freiburg, Germany, August 30–September 2, 2022