Preliminary results of STAAR, a Phase I/2 study of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease and long-term follow-up

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Introduction

Fabry Disease

- Fabry disease (FD) is a lysosomal storage disease caused by pathogenic mutations in the *GLA* gene leading to deficiency of the lysosomal enzyme, alpha-galactosidase A (α-Gal A), and accumulation of globotriaosylsphingosine (lyso-Gb3).
- Treatments for FD are limited and require repeated intravenous (IV) infusions impacting patient safety and quality of life.
- Despite treatment, patients may still experience disease progression and organ damage.

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

- Isaralgagene Civaparvovec (ST-920) is an investigational gene therapy using a recombinant AAV2/6 vector containing human *GLA* cDNA and is intended to be administered as a one-time IV infusion.
- After infusion, the functional gene is delivered to the liver where liver cells 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.
- STAAR is an ongoing first-in-human phase 1/2 clinical study evaluating the safety, tolerability, and preliminary efficacy of ascending doses of ST-920.
- After follow-up for 52 weeks in STAAR, subjects are invited to transition into a 4-year long-term follow-up (LTFU) study.

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) with dose escalation and dose expansion phases.
- 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.
- Safety and efficacy data of each cohort were reviewed by a safety monitoring committee (SMC) prior to dose escalation.
- The dose escalation phase includes men with classic Fabry disease.
- The subsequent expansion phase, at the 5.0E+13vg/kg dose per SMC endorsement, is composed of five cohorts: females, subjects with Fabry-associated cardiac and renal disease, and subjects positive and negative for Anti-α-Gal A antibodies.
- 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.

Results

Baseline Subject Characteristics

- Here we present preliminary data (cutoff July 21, 2022) from the 4 ascending dose cohorts.
- Nine 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 (0.5E+13 vg/kg), 2 subjects in Cohort 2 (1.0E+13 vg/kg), 3 subjects in Cohort 3 (3.0E+13 vg/kg), and 2 subjects in Cohort 4 (5.0E+13 vg/kg).
- The 4 subjects in Cohort 1 (n=2) and Cohort 2 (n=2) completed the dose escalation phase with 1 year of follow-up and are now enrolled in the LTFU study.

Table 1. Baseline Subject Characteristics

	Cohort 1 (n=2) 0.5e13 vg/kg		Cohort 2 (n=2) 1.0e13 vg/kg		Cohort 3 (n=3) 3.0e13 vg/kg			Cohort 4 (n=2) 5.0e13 vg/kg	
	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Subject 7	Subject 8	Subject 9
Age (years)	48	25	42	22	39	42	51	49	40
ERT	Agalsidase beta	Pseudo-naïve to ERT	Pseudo-naïve to ERT	Agalsidase beta	Agalsidase beta	Agalsidase beta	Agalsidase beta	No (Naïve)	No (Naïve)
Plasma α-Gal A activity (nmol/h/mL)*	1.54	Below LOQ	Below LOQ	2.24	0.91	Below LOQ	Below LOQ	0.96	Below LOQ
Plasma lyso-Gb3 (ng/mL)*	22.1	18.1	83.2	11.1	32.9	1.91	16.3	16.9	167
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†	Depression Ventricular tachycardia Hearing loss Neuropathic pain	Tinnitus Mild ventricular hypertrophy Acroparesthesia†	Mild ventricular wall thickness
Renal function (eGFR; mL/min/1.73 m²)‡	101.4	111.4	112.9	100	91.5	80	63.8	45.4	82.1
Pre-existing α-Gal A Abs	Positive	Negative	Positive	Positive	Positive	Negative	Negative	Negative	Negative
Mutation	G261D	T141I	W340R	S297Y	Q283X	N215S	c.801+3A>G	P362L	T141I
Length of follow-up	23 months	22.2 months	17.6 months	14.1 months	40.3 weeks	26.3 weeks	16.4 weeks	16.4 weeks	14.1 weeks

*The time point immediately preceding ST-920 administration was presented as the baseline value.
†Burning, tingling, or numbness in the extremities.
‡eGFR (mL/min/1.73 m²) was calculated using the CKD-EPI.
Ab, antibody; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LOQ, limit of quantitation; lyso-Gb3, globotriaosylsphingosine.

Results

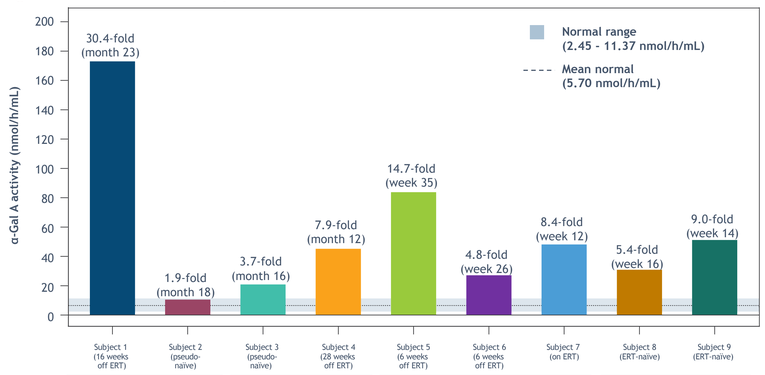
Safety and Tolerability

- ST-920 continues to be generally well tolerated, with no treatment-related serious adverse events.
- Seventeen treatment-related AEs occurred in 5 subjects; all were Grade 1 (mild), except one Grade 2 pyrexia (moderate).
- No subjects have been treated with steroids, either prophylactically or reactively.

Plasma α-Gal A Activity and Lyso-Gb3 Concentration

- Sustained, elevated α-Gal A activity was observed through the last sampling point for all nine subjects. (**Figure 1**)
- The first four subjects in the LTFU maintained elevated α-Gal A activity for one year or more.

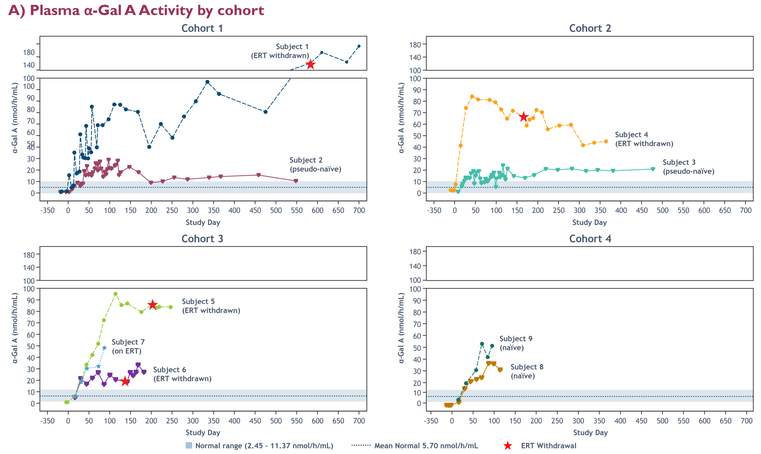
Figure 1. Plasma α-Gal A Activity at Cutoff



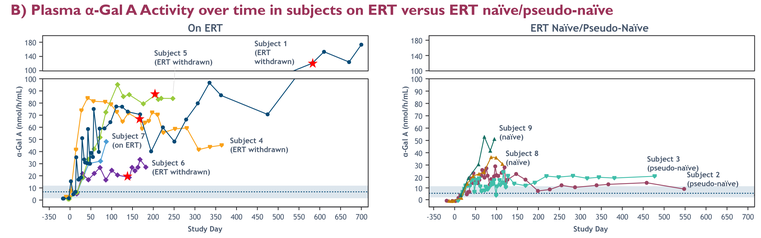
Biomarker results were evaluated as of the cutoff date of July 21, 2022.
*Fold change was calculated at last measured time point. α-Gal A activity was measured using a 3-hour reaction time and is presented in nmol/h/mL. For Subject 7 sampling was at ERT trough. Normal range and mean were determined based on healthy male individuals. α-Gal A, alpha galactosidase A; ERT, enzyme replacement therapy; LTFU, long-term follow-up.

Figure 2. Plasma α-Gal A Activity over time

A) Plasma α-Gal A Activity by cohort

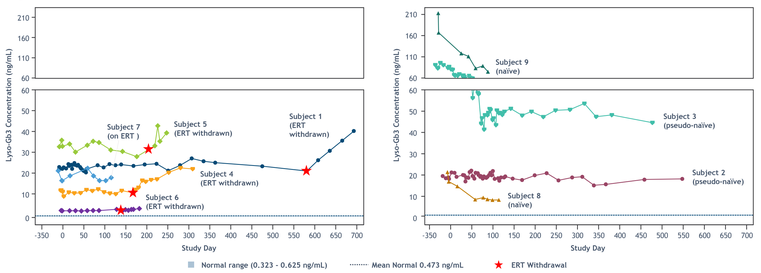


B) Plasma α-Gal A Activity over time in subjects on ERT versus ERT naïve/pseudo-naïve



- All subjects demonstrated elevated and sustained α-Gal A activity in each cohort **(Figure 2A)**.
- α-Gal A activity increased rapidly after dosing and remained elevated until the last sampling timepoint.
- α-Gal A activity remained high after ERT withdrawal in all four subjects.
- Higher levels of α-Gal A activity were reported in the Cohort 4 ERT-naïve subjects compared to the pseudo-naïve subjects in Cohorts 1 and 2. **(Figure 2B)**

Figure 3. Plasma Lyso-Gb3 Concentration



- Subjects with substantially elevated levels of plasma lyso-Gb3 (>60 ng/ml) pre-treatment showed significant decreases in lyso-Gb3 plasma concentrations post ST-920 dosing (**Figure 3**).
  - Subject 3 (pseudo-naïve) showed an approximately 40% reduction from baseline within 10 weeks after dosing that was maintained through Month 15.
  - Subject 9 (naïve) showed an approximately 55% reduction from baseline within 14 weeks of dosing.
- Several subjects experienced some increases in plasma lyso-Gb3 levels after ERT withdrawal. In these subjects α-Gal A activity remained elevated, and no subject has resumed ERT.

Conclusions and Next Steps

- Up to the data cutoff date of July 21, 2022, isaralgagene civaparvovec (ST-920) was generally well tolerated, with no treatment-related AEs that were serious or higher than Grade 1, with the exception of one Grade 2 pyrexia.
- No subjects have been treated with steroids, either prophylactically or reactively.
- Elevated α-Gal A activity has been maintained in all subjects dosed with ST-920, ranging from nearly 2-fold to 30-fold of mean normal, up to 23 months post infusion for the longest treated subject.
- α-Gal A activity increased rapidly after dosing and remained elevated until the last sampling timepoint.
- Four subjects were withdrawn from enzyme replacement therapy (ERT) and demonstrated significantly elevated levels of α-Gal A activity, up to 28 weeks post withdrawal.
- Higher levels of α-Gal A activity were reported in the Cohort 4 ERT-naïve subjects compared to the pseudo-naïve subjects in Cohorts 1 and 2.
- Two subjects with substantially higher elevations in plasma lyso-Gb3 pre-treatment showed a reduction of approx. 40% and 55% from baseline in lyso-Gb3 level after ST-920 dosing.
- Several subjects experienced some increases in plasma lyso-Gb3 levels after ERT withdrawal. In these subjects α-Gal A activity remained elevated, and no subject has resumed ERT.
- Since the cutoff date, one additional subject was withdrawn from ERT.
- The Phase 1/2 STAAR study has progressed into the dose expansion phase, with four subjects dosed, including the first female subject.
- Based on these encouraging emerging data, phase 3 planning has been initiated.

References

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Acknowledgments

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Disclosures

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