Poster #146

Isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease: Updated results from an ongoing Phase 1/2 study (STAAR)

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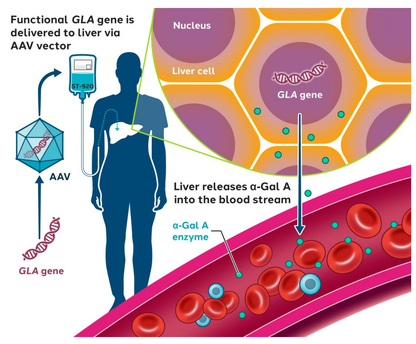
Introduction

- Fabry disease is a progressive, multi-organ, 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).
- Isaralgagene civaparvovec (ST-920) is an investigational gene therapy using a recombinant AAV2/6 vector containing human GLA cDNA designed to produce continuous, liver-specific α-Gal-A expression.
- A gene therapy approach offers potential advantages:
  - Convenient one-time administration
  - Eliminate need for repeated enzyme replacement therapy (ERT) infusions
  - Durable efficacy
  - Low immunogenicity
- This Phase 1/2 open-label, multicenter study (STAAR) evaluate ST-920 in adults with symptomatic Fabry Disease (NCT04046224).



Study design

Key eligibility criteria

- Age ≥18 with symptomatic Fabry disease
  - ERT-naïve or pseudo-naïve (no ERT in prior 6 months)
  - On ERT
- Estimated glomerular filtration rate (eGFR) ≥40 mL/min/1.73m^2
- No neutralizing antibodies to AAV6

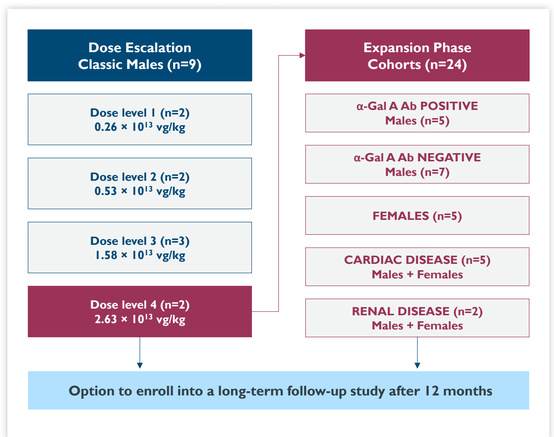
Primary objective

- Safety and tolerability of ST-920

Other objectives

- α-Gal A activity and change in plasma lyso-Gb3
- Impact on ERT administration
- Renal and cardiac function
- Patient-reported outcomes and Quality of Life (QoL) scores
- Immunogenicity

Figure 1: STAAR study design



Study schema (Figure 1)

- Four dose levels were evaluated in the dose escalation phase (n=9); the recommended dose for further evaluation was 2.63 x 10^{13} viral genomes per kilogram (vg/kg) (measured by digital droplet PCR; same as 5 x 10^{13} by quantitative PCR)
- 24 subjects were subsequently enrolled into 5 expansion phase cohorts
- All subjects were offered the option to enroll into a long-term follow-up study after 12 months
- At the discretion of the Investigator, subjects receiving ERT were withdrawn from ERT ≥8 weeks following ST-920 administration

Results

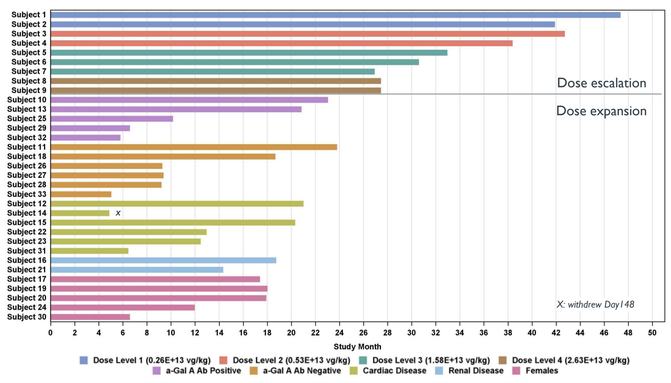
- Data on 33 subjects (data cutoff date: 12 Sep 2024) are reported in this analysis. Enrollment and dosing is complete.
- The baseline characteristics of all subjects are shown in Table 1

Table 1: Baseline characteristics: Dose escalation and dose expansion phases

	Dose escalation (n=9)	Dose expansion (n=24)	All (n=33)
Age, median (range)	42 (22-50)	41.5 (18-67)	42 (18-67)
Sex (M:F)	9:0	14:10	23:10
ERT status (n,%):			
• Naïve	2 (22%)	7 (29%)	9 (27%)
• Pseudo-naïve	2 (22%)	4 (17%)	6 (18%)
• On ERT	5 (56%)	13 (54%)	18 (55%)
Baseline Fabry symptoms (n,%):			
• Cornea verticillata	4 (44%)	15 (63%)	20 (61%)
• Paresthesia	3 (33%)	7 (29%)	10 (30%)
• Anhidrosis	1 (11%)	5 (21%)	6 (18%)
• Angiokeratoma	2 (22%)	9 (38%)	11 (33%)
eGFR$_{CKD-EPI}$ category, n (%):			
• >90 ml/min/1.73 m^2	4 (44%)	15 (63%)	19 (58%)
• 60-90 ml/min/1.73 m^2	4 (44%)	6 (25%)	10 (30%)
• 40-<60 ml/min/1.73 m^2	1 (11%)	3 (13%)	4 (12%)

Figure 2: Follow-up in months (dose escalation and dose expansion cohort)

- Median duration of follow-up: 18 months (20 weeks – 47.3 months)
- 23 subjects have ≥ 12 months of follow-up



Safety

- ST-920 was generally well-tolerated with the majority of Adverse Events being grade 1-2 in nature, as of the 12 September 2024 cut-off date
- No LFT elevations requiring steroids
- TESAEs were reported in 4 subjects, all Grade 2 or Grade 3:
  - Left arm pain, non-cardiac chest pain, sepsis, stroke, shoulder enthesopathy
- No AEs led to study discontinuation
- No deaths

Table 2: Summary of treatment-emergent AEs in >3 of 33 subjects

AE by preferred term	Treated subjects (n=33)	
	All grades	Grade 3-4
Pyrexia	20 (60.6%)	1 (3.0%) (G3)
COVID-19	12 (36.4%)	0
Nasopharyngitis	11 (33.3%)	0
Headache	12 (36.4%)	0
Fatigue	9 (27.3%)	0
Nausea	9 (27.3%)	0
Cough	5 (15.2%)	0
Diarrhea	5 (15.2%)	0
Myalgia	5 (15.2%)	1 (3.0%) (G3)
Hypotension	4 (12.1%)	0
Urinary tract infection	4 (12.1%)	0
Paresthesia	4 (12.1%)	0
Chills	4 (12.1%)	0

Acknowledgments

We would like to thank the patients, their families, the investigators and their study teams for their participation in this study. This study was sponsored by Sangamo Therapeutics.

Efficacy

- Sustained supraphysiological α-Gal A activity up to **27 months** for those naïve/pseudo-naïve subjects receiving the top dose (2.63x10^{13} vg/kg) and **42 months** for all naïve/pseudo-naïve subjects, independent of dose (Fig. 3a)
- Largest reductions in plasma lyso-Gb3 in subjects with highest levels at baseline. Long-term stabilization of lyso-Gb3 levels (Fig. 3b).

Figure 3: Supraphysiological levels of Plasma α-Gal A and reductions in lyso-Gb3 in naïve/pseudo-naive subjects receiving 2.63×10^{13} vg/kg (n=13)

Fig 3a: Plasma α-Gal A activity

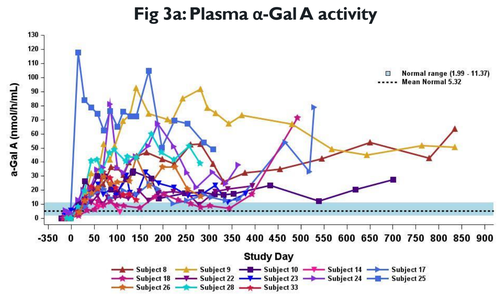
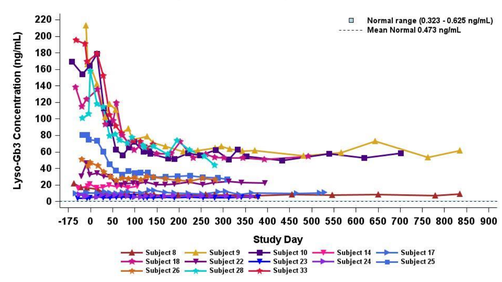


Fig 3b: Plasma lyso-Gb3



- 17 out of 18 ERT subjects withdrawn from ERT as of the data cut-off. The remaining one subject was withdrawn after the Sep'24 data cut. All 18 out of 18 ERT subjects remain off ERT.
- Plasma lyso-Gb3 levels remained stable following ERT withdrawal for up to **19 months** for ERT subjects receiving the top dose (2.63x10^{13} vg/kg) and **33 months** for all ERT subjects, independent of dose (Fig 4b)

Figure 4: Sustained increased levels of plasma α-Gal A and stable levels of lyso-Gb3 following ERT withdrawal in ERT-treated subjects receiving 2.63×10^{13} vg/kg (n= 13)

Fig 4a: Plasma α-Gal A activity

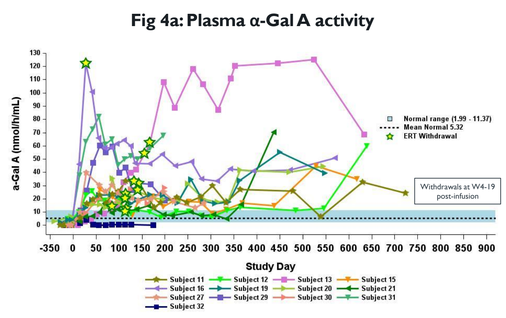


Fig 4b: Plasma lyso-Gb3

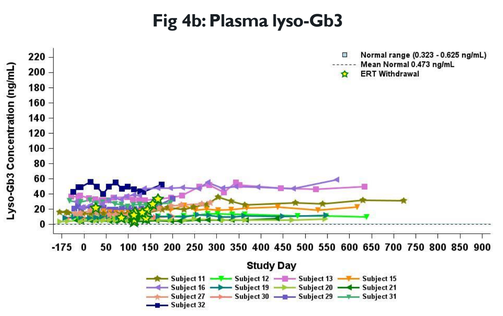


Table 3: For the 23 subjects with at least 1-year follow-up, a positive mean eGFR slope was observed

eGFR slope at 1 year; N=23	
Mean (SD), (95% CI)	3.061 (5.1), (0.863, 5.258)

eGFR slope for each subject is estimated using linear regression and then summarized

Significant improvement seen in disease severity, QoL and GI symptoms

Table 4: FOS-MSSI scores in subjects with ≥12 m follow-up (n=23)

Subject	ERT status at Baseline	FOS-MSSI category Baseline	FOS-MSSI category Week 52	FOS-MSSI category Week 104	FOS-MSSI category Year 3	FOS-MSSI category Year 4
1	ERT	Moderate	Moderate		Moderate	Mild
2	Pseudo-naive	Mild	Mild	Mild	Mild	
3	Pseudo-naive	Moderate	Moderate	Mild	Mild	
4	ERT	Mild	Mild	Mild	Mild	
5	ERT	Moderate	Mild	Moderate		
6	ERT	Moderate	Mild	Mild	Mild	
7	ERT	Severe	Moderate	Moderate		
8	Naive	Moderate	Mild	Mild		
9	Naive	Moderate		Moderate		
10	Pseudo-naive	Moderate	Moderate	Moderate		
11	ERT	Moderate	Moderate	Moderate		
12	ERT	Mild	Mild	Mild		
13	ERT	Mild	Mild			
15	ERT	Mild	Mild			
16	ERT	Moderate	Moderate			
17	Naive	Moderate	Mild			
18	Naive	Moderate	Moderate			
19	ERT	Mild	Moderate			
20	ERT	Moderate	Moderate			
21	ERT	Moderate	Mild			
22	Naïve	Mild	Mild			
23	Naive	Mild	Mild			
24	Pseudo-naive	Moderate	Moderate			

FOS-MSSI:

- At 12m, 15/22 (68 %) of subjects improved their total MSSI score
- 7 subjects (including 4 on ERT) improved their FOS-MSSI category

SF-36 (12 mo):

- General Health score: +10.6 (n=21; p-value=0.0020)
  - +3-5 change is considered a minimal clinically important difference (Steward AL et al., (1989)
- Statistically significant improvement in physical component, bodily pain, physical, vitality, social function, and emotional scores

GSRS (GI Symptom Rating Scale) (12 mo):

- Statistically significant improvement in GSRS score, Abdominal Pain, Indigestion, Diarrhoea and Constipation Scores, n=22

Reduction or elimination of antibodies against α-Gal A

Table 5: Anti-α-Gal A total and neutralizing antibody titers

	Anti-α-GalA Total Ab titer		Anti-α-GalA NAb titer	
	Baseline	On-study	Baseline	On-study
Subject 1	1280	160	160	Undetectable (W36)
Subject 3	160	Undetectable (W24)	0	-
Subject 4	160	Undetectable (W52)	0	-
Subject 5	10240	1280	320	160
Subject 10	80	Undetectable (W4)	10	Undetectable (W4)
Subject 13	5120	320	160	10
Subject 16	2560	640	40	Undetectable (W52)
Subject 25	160	Undetectable (W4)	160	Undetectable (W4)
Subject 31	80	Undetectable (W12)	10	Undetectable (W4)
Subject 32	20480	20480	640	320

- Immunogenicity remains an issue with ERT, leading to continuing organ impairement
- 10 subjects had measurable titers of total antibodies (Ab) or neutralizing antibodies (NAb) against α-Gal A associated with ERT at baseline
- After ST-920 treatment, total Ab or NAb titers decreased markedly in 9 subjects and became undetectable in 7 (70%)
- ST-920 treatment did not induce anti-α-Gal A antibodies in seronegative subjects

Conclusions

- ST-920 gene therapy was well-tolerated with an **excellent safety profile** in this population of adults with symptomatic Fabry disease
  - Mainly Grade 1 and 2 Adverse Events and no discontinuation based on ST-920
  - No prophylactic steroids or other immunomodulatory agents administered. No LFT elevations requiring steroids
- **Durable efficacy** was demonstrated with supraphysiological α-Gal A activity up to **27 months** for those receiving the top dose (2.63x10^{13} vg/kg) and **47 months** for all subjects independent of dose
- **Positive mean eGFR slope** observed in the 23 subjects that have reached 1-year follow-up, indicating improvements in renal function
- **Clinically and statistically significant QOL improvements**
  - 68 % improvement in FOS-MSSI
  - Improvement in SF-36 scores
  - Improvements in gastrointestinal symptoms
- All 18 subjects who discontinued ERT **remain off ERT**, for up to 33 months
- **Total or neutralizing α-Gal A antibodies decreased** markedly in 9 subjects and became undetectable in 7 (70%)
- **ST-920 has potential as a one-time, durable treatment option for Fabry disease that can improve patient outcomes**

References:

1. Stewart AL, Greenfield S, Hays RD, Wells K, Rogers WH, Berry SD, et al. Functional status and well-being of patients with chronic conditions. Results from the medical outcomes study. JAMA. 1989;262:907–13

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