Poster #145

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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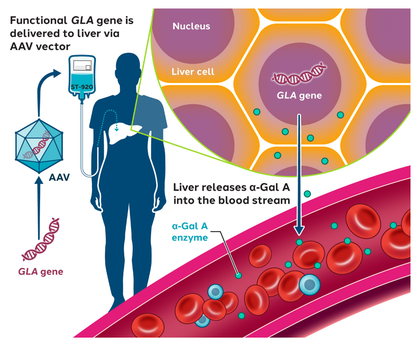
Introduction

- 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) evaluates 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

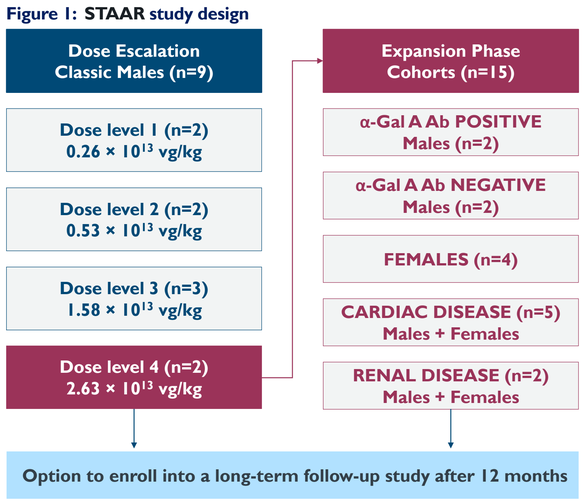
Primary objective

- 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 (+ renal Gb3 inclusions)
- 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)
- 15 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 (m).
- At the discretion of the Investigator, subjects receiving ERT were withdrawn from ERT ≥8 weeks (wks) following ST-920 administration.

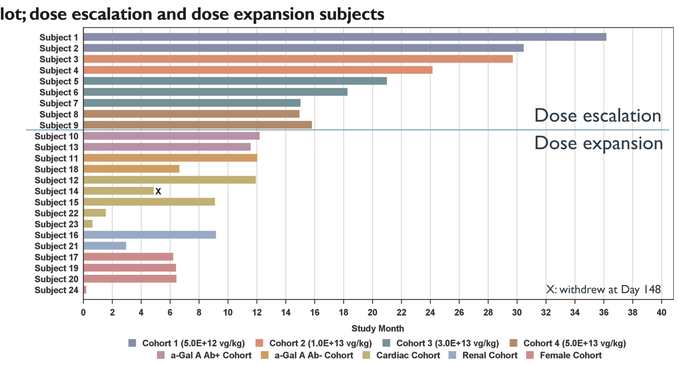
Results

Data on 24 patients (data cutoff date: 19 Sep 2023) are reported in this analysis; the median duration of follow-up for all patients was 51.1 weeks (range: 0.9 wk – 36.2 m; Fig 2).
The baseline characteristics of all patients are shown in Table 1.

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

	Dose escalation (n=9)	Dose expansion (n=15)	All (n=24)
Age, median (range)	42 (22-50)	45 (21-67)	44 (21-67)
Sex (M:F)	9:0	6:9	15:9
ERT status (n,%)			
• Naïve	2 (22%)	4 (27%)	6 (25%)
• Pseudo-naïve	2 (22%)	3 (20%)	5 (21%)
• On ERT	5 (56%)	8 (53%)	13 (54%)
Baseline Fabry symptoms (n,%)			
• Cornea verticillata	4 (44%)	8 (53%)	12 (50%)
• Acroparesthesia	3 (33%)	3 (20%)	6 (25%)
• Anhidrosis	1 (11%)	2 (13%)	3 (13%)
• Angiokeratoma	2 (22%)	7 (47%)	9 (38%)
eGFR$_{CKD-EPI}$ category (n,%)			
• >90 ml/min/1.73 m^2	5 (56%)	9 (60%)	14 (58%)
• 60-90 ml/min/1.73 m^2	3 (33%)	3 (20%)	6 (25%)
• 40-<60 ml/min/1.73 m^2	1 (11%)	3 (20%)	4 (17%)

Figure 2: Swimmer plot; dose escalation and dose expansion subjects



Safety

- ST-920 was generally well-tolerated with majority of adverse events (AEs) being grade 1-2
- As of the 19 Sep 2023 cutoff date, 3 subjects (12%) experienced post-infusion hypotension:
  - Grade 2, steroids administered (n=2)
  - Grade 1, saline bolus administered (n=1)
- No liver function test (LFT) elevations requiring steroids occurred
- Prophylactic steroids/other immunosuppressive agents were not given
- TESAEs (treatment-emergent serious AEs) were reported in 4 subjects: left arm pain (0.53×10^{13} vg/kg); sepsis (1.58×10^{13} vg/kg); enthesopathy, stroke/ischemic stroke (2.63×10^{13} vg/kg)
- No AEs led to study discontinuation

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

AE by preferred term	Treated subjects (n=24)	
	All grades	Grade 3-4
Pyrexia	15 (63%)	1 (4%) (G3)
Headache	9 (38%)	0
COVID-19	9 (38%)	0
Fatigue	7 (29%)	0
Nasopharyngitis	6 (25%)	0
Diarrhea	4 (17%)	0
Hypotension	4 (17%)	0
Nausea	4 (17%)	0
Arthralgia	3 (13%)	0
Viral infection	3 (13%)	0
Myalgia	3 (13%)	1 (4%) (G3)
Neck pain	3 (13%)	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

In ERT naïve/pseudo-naive subjects receiving 2.63 x 10^{13} vg/kg, sustained supraphysiological α-Gal A activity was seen for up to nearly 500 days (Fig 3a).
Plasma lyso-Gb3 levels stabilized long-term, with the largest reductions occurring in subjects with the highest levels at baseline (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=9)

Fig 3a: Plasma α-Gal A activity

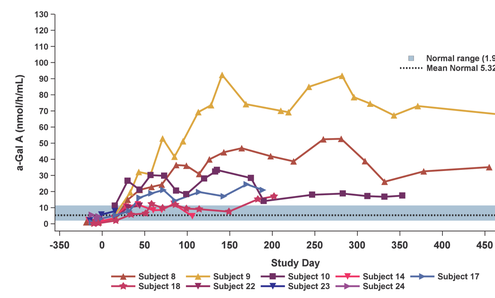
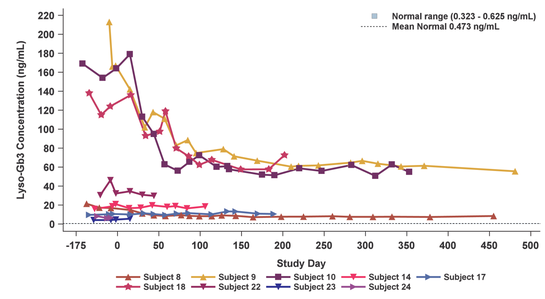


Fig 3b: Plasma lyso-Gb3



All 12 subjects withdrawn from ERT remain off ERT; 11 maintain sustained supraphysiological levels of α-Gal A activity for up to ~19 m (1 sustained physiological levels) (Fig 4a).
Plasma lyso-Gb3 levels remained stable following ERT withdrawal for up to 1 year (last data timepoint) (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=8)

Fig 4a: Plasma α-Gal A activity

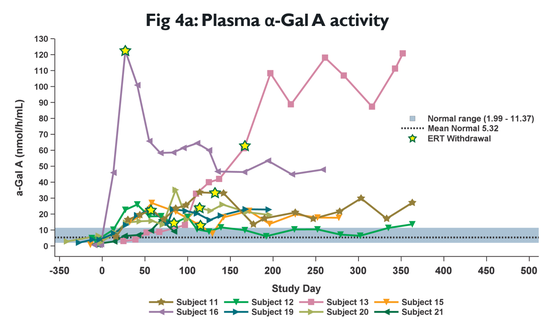
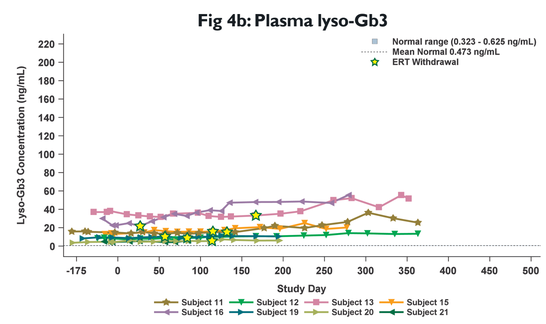


Fig 4b: Plasma lyso-Gb3

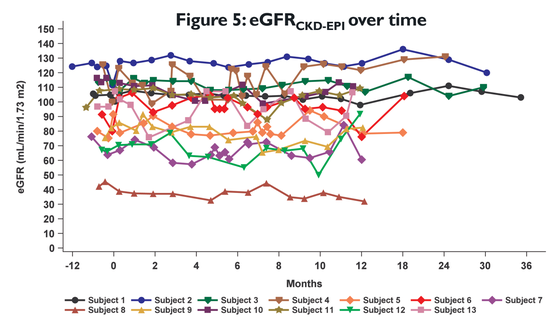


In subjects with ≥12 m follow-up (n=13)

1. Renal function remained stable

- Median eGFR at baseline: 96.7 mL/min/1.73m^2
- Mean annualized eGFR slope: **-0.915** mL/min/1.73m^2/year (95% CI: -4.1, 2.3)

Figure 5: eGFR$_{CKD-EPI}$ over time



2. Significant improvement seen in disease severity, QoL and GI symptoms

Table 3: FOS-MSSI scores in subjects with ≥12 m follow-up (n=13)

Subject	ERT status at Baseline	FOS-MSSI category Baseline	FOS-MSSI category Week 52
1	ERT	Moderate	Moderate
2	Pseudo-naive	Mild	Mild
3	Pseudo-naive	Moderate	Moderate
4	ERT	Mild	Mild
5	ERT	Moderate	**Mild**
6	ERT	Moderate	**Mild**
7	ERT	Severe	**Moderate**
8	Naive	Moderate	**Mild**
9	Naive	Moderate	Moderate
10	Pseudo-naive	Moderate	Moderate
11	ERT	Moderate	Moderate
12	ERT	Mild	Mild
13	ERT	Mild	Mild

FOS-MSSI (Fabry Outcome Survey - Mainz Severity Score Index[1]):

- Mean change from baseline at 12 m (age-adjusted score): **-3.96** (95% CI: -7.4,-0.5; p=0.0269*)
- 9/13 (69%) improved their total MSSI score vs baseline
- 4 subjects (including 3 on ERT) improved their disease category (Table 3)
- Improvements in each of the 4 MSSI subsections were observed
- 6/8 (75%) subjects initially on, then withdrawn from ERT, improved their scores by -3.5 to -14 points

SF-36: Mean change from baseline at 12 m

- General Health score: **+10.5** (95% CI: 2.3, 18.6; p=0.0158), where +3-5 change in an SF-36 score is a minimal clinically important difference[2]
- Physical Component score: **+4.395** (95% CI: 1.1, 7.7; p=0.0140)

GSRS (Gastrointestinal [GI] Symptom Rating Scale):

- Mean change from baseline at 12 m: **-0.26** (95% CI: -0.5, -0.0; p=0.0226)

*All p-values are nominal p-values

Reduction/elimination of antibodies against α-Gal A

- Progressive organ impairment linked to immunogenicity remains an issue with ERT
- Post-ST-920, total antibody (Ab) or neutralizing Ab (Nab) titers decreased markedly in 7 subjects with measurable titers of total Ab or NAb against α-Gal A at baseline and became undetectable in 5 (71%) (Table 4)
- ST-920 treatment did not induce anti-α-Gal A antibodies in seronegative subjects

Table 4: 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	-
Subject 13	5120	320	160	10
Subject 16	2560	Undetectable (W36)	40	-

Conclusions

- ST-920 gene therapy was well-tolerated with an excellent safety profile in this population of adults with symptomatic Fabry disease
- Durable efficacy was demonstrated with supraphysiological levels of α-Gal A activity maintained for up to 3 years for the longest-treated patient
- All 12 subjects who discontinued ERT remain off ERT for up to 19 months
- Compared to baseline, in 13 subjects with ≥12 months of follow-up:
  - Renal function remained stable
  - There was significant improvement in FOS-MSSI disease severity score, with 38% of subjects on ERT improving in disease severity category
  - Significant improvement in SF-36 QoL and GSRS GI symptom scores was reported
- Benefits on immunogenicity: Total or neutralizing α-Gal A antibodies decreased markedly in 7 subjects and became undetectable in 5 (71%)
- ST-920 has potential as a one-time, durable treatment option for Fabry disease that can improve patient outcomes.

References

1. Hughes DA, et al. Mol Genet Metab. 2010;101:219.
2. Arends M, et al. Orphanet J Rare Dis. 2015;10: 77.

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