Isaralgagene civaparvovec (ST-920) shows positive mean annualized eGFR slope in adults with Fabry disease: Topline results from the registrational Phase 1/2 STAAR gene therapy study and long-term follow-up study

Poster # 36

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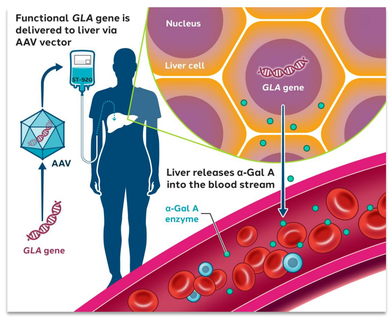
Introduction

- Fabry disease is a progressive, multi-organ, lysosomal 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)
- Hypertrophic cardiomyopathy, myocardial infarction, arrhythmias, and diastolic heart failure
- 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)

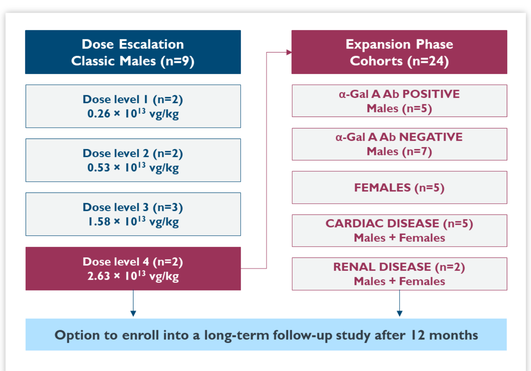


Study design

Key eligibility criteria
- Age ≥18 with symptomatic Fabry disease
  - ERT-naïve or pseudo-naïve (no ERT in prior 6 months)
  - On ERT
- 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 QoL scores
- Immunogenicity



Statistical methods
- Two methods were employed to estimate the mean eGFR slope and its 95% confidence interval (CI). First, individual eGFR slopes at Week 52/104 were estimated using a linear regression model in a two-step process. Separately, a mixed model with random intercept and random slope (RIRS) was used for estimation.

Study schema
- Four dose levels were evaluated in the dose escalation phase (n=9); the recommended dose for further evaluation was 2.63 x 10^{13} vector genomes per kilogram (vg/kg) (measured by digital droplet PCR; same as 5 x 10^{13} vg/kg by quantitative PCR)
- 24 participants were subsequently enrolled into 5 expansion phase cohorts
- All participants were offered the option to enroll into a long-term follow-up study after 12 months
- At the discretion of the Investigator, participants receiving ERT were withdrawn from ERT ≥4 weeks following ST-920 administration

Baseline characteristics and follow-up

	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	7	9
• Pseudo-naïve	2	4	6
• On ERT	5	13	18
Baseline Fabry symptoms (n):			
• Cornea verticillata	4	10	14
• Paresthesia	3	7	10
• Anhidrosis	1	5	6
• Angiokeratoma	2	9	11
eGFR$_{CKD-EPI}$ category (n):			
• >90 ml/min/1.73 m^2	4	13	17
• 60-90 ml/min/1.73 m^2	4	8	12
• 40-<60 ml/min/1.73 m^2	1	3	4

- Longest treated participant has achieved 4.5 years follow-up as of the data cut-off date
- Median duration of follow-up was 24 months (21.1 weeks – 54.3 months)
- 32 participants have ≥12 months of follow-up
- 19 participants have ≥ 24 months of follow-up
- Participant 14 withdrew from the study at Day 148 post-dosing, due to patient decision

Favorable safety profile

Summary of treatment-emergent AEs in ≥10% of participants

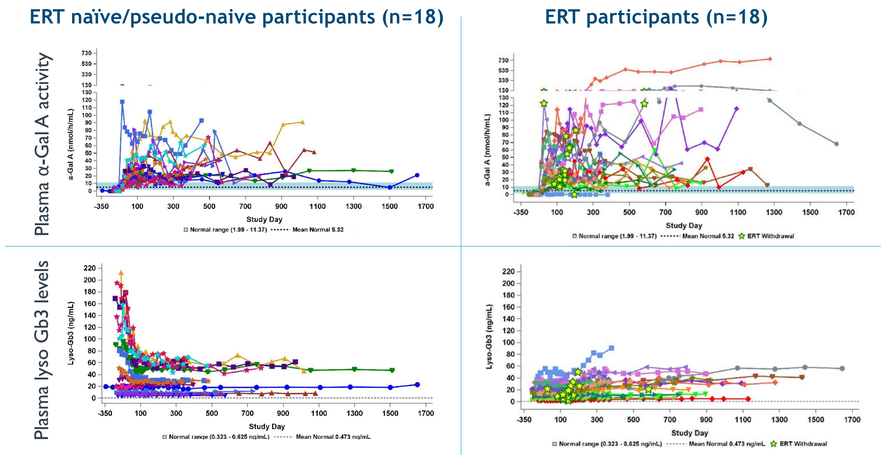
AE by preferred term	Treated participants (n=33)		AE by preferred term	Treated participants (n=33)	
	All grades	Grade 3-4		All grades	Grade 3-4
Pyrexia	20 (60.6%)	1 (3.0%) (G3)	**Dizziness**	5 (15.2%)	0
COVID-19	12 (36.4%)	0	**Cough**	5 (15.2%)	0
Nasopharyngitis	11 (33.3%)	0	**Abdominal Pain**	4 (12.1%)	0
Headache	10 (30.3%)	0	**Palpitations**	4 (12.1%)	0
Fatigue	9 (27.3%)	0	**Hypotension**	4 (12.1%)	0
Nausea	9 (27.3%)	0	**Infusion Related Reaction**	4 (12.1%)	0
Diarrhea	6 (18.2%)	0	**Urinary Tract Infection**	4 (12.1%)	0
Paresthesia	5 (15.2%)	0	**Dyspnoea**	4 (12.1%)	0
Myalgia	5 (15.2%)	1 (3.0%) (G3)			

- ST-920 was generally well tolerated, with the majority of AEs being Grade 1-2. Four participants experienced TESAEs of Grade 2 or 3: Left arm pain, non-cardiac chest pain, sepsis, stroke, and a single treatment related event of shoulder enthesopathy – all resolved without sequalae
- LFT elevation events (all Grade 1 with one requiring short term corticosteroid) resolved without clinical sequalae
- No TMA, complement activation adverse events or thrombocytopenia were observed
- No AEs led to study discontinuation and there were no deaths

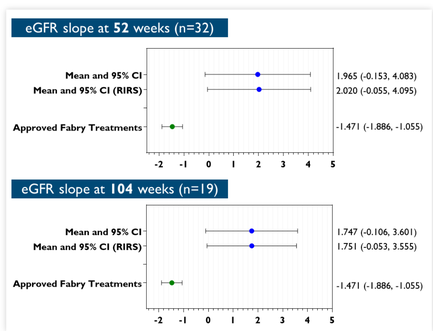
Durable α-Gal A activity and lyso-Gb3 control

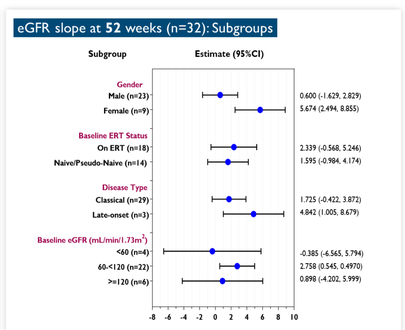
ERT Naïve/pseudo naïve participants (n=15)
All ERT naïve/pseudo naïve participants demonstrated normal to supraphysiological levels of plasma α-Gal A and reductions in lyso-Gb3

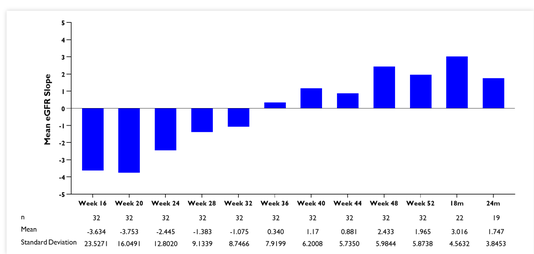
ERT participants (n=18)
17 of 18 participants on ERT have sustained elevated levels of plasma α-Gal A and stable levels of lyso-Gb3 following ERT withdrawal



Positive mean annualized eGFR slope: 52 weeks

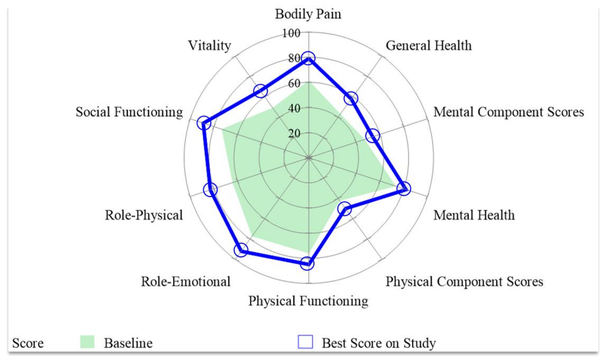






- Improvements in renal function observed at 52 weeks (n=32) and 104 weeks (n=19)
- Supportive mean annualized eGFR slopes across subgroups, a consistent effect across all participants
- Sustained renal function improvement demonstrated over 24 months, with improvement seen as early as 24 weeks post ST-920 administration

Quality of life and disease severity



- **QoL SF-36 (52 weeks):** Statistically significant and clinically meaningful improvements in general health, physical component, bodily pain, role-physical, vitality, and social functioning scores
- **QoL GSRS (52 weeks):** Statistically significant improvement in GSRS score and diarrhea
- **Disease Severity FOS-MSSI:** Age-adjusted score mean change (95% CI) from baseline at Week 52 was -4.21 [-6.2, -2.2], p=0.0002
- Nine participants (five on ERT) improved their disease category (mild, moderate, severe) from baseline compared to last assessment. 14 participants were mild both at baseline and at last assessment.

Cardiac* & immunogenicity results

Cardiac
- Cardiac measures were generally stable:
  - End-diastolic and end-systolic volume, LVM, LVMI and LVGLS
- T1 and T2 mapping were generally stable
- Ejection Fraction (%) remained stable over one year, with an increasing trend observed in 50% of participants who reached Week 104Cardiac markers were generally stable: Troponin-T and NT-ProBNP

α-Gal A Immunogenicity
- Immunogenicity remains an issue with ERT leading to continuing organ impairment
- 10 participants had measurable titers of total antibodies (TAb) or neutralizing antibodies (NAb) against α-Gal A associated with ERT at baseline
- After ST-920 treatment, TAb or NAb titers decreased markedly in nine participants and became undetectable in eight (80%)
- ST-920 treatment did not induce anti-α-Gal A antibodies in seronegative participants

***Poster:** Isaralgagene civaparvovec (ST-920) shows stable cardiac function over one year in patients with Fabry disease: Results from the registrational Phase 1/2 STAAR gene therapy study*

Conclusions

Totality of data supports the potential for ST-920 as a one-time, durable treatment of underlying pathology of Fabry disease to provide meaningful, multi-organ, clinical benefits above current standards of care
- ST-920 gene therapy was well-tolerated with an **excellent safety profile**
- **A positive mean annualized eGFR slope** indicating improvements in renal function
- **Durable elevated α-Gal A activity** observed up to 4.5 years for the longest treated participant
- All participants on ERT **withdrew from ERT** and remained off ERT as of the cutoff date
- **Stable cardiac function** was observed over one and two years*
- Clinically and statistically significant **Quality of Life improvements** were observed
- **Total and/or neutralizing α-Gal A antibodies decreased** markedly
- Our team plans to **complete submission of a BLA** for ST-920 in 2026

Acknowledgments

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

Data Cut-off 10Apr2025
ERT: Enzyme Replacement Therapy; AE: Adverse Event, CI: Confidence Interval, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, eGFR: estimated Glomerular Filtration Rate, ERT: Enzyme Replacement Therapy, FOS-MSSI: Fabry Outcome Survey-Mainz Severity Score Index, GLA: galactosidase alpha gene, GSRS: Gastrointestinal Symptoms Rating Scale, LTF: Liver Function Test, NAb: Neutralizing Antibody, NT-ProBNP: N-terminal pro b-type Natriuretic Peptide, QoL: Quality of Life, SF-36 Short Form-36, TAb: Total Antibody, TESAE: Treatment Emergent Serious Adverse Event, TMA: Thrombotic microangiopathy.

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