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

Poster # LB-53

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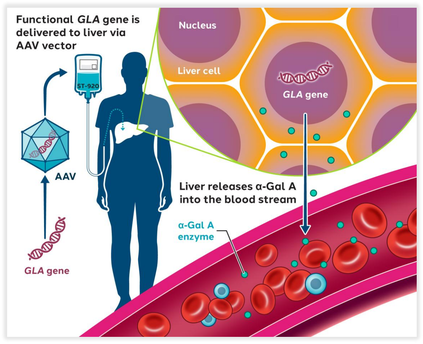
Introduction

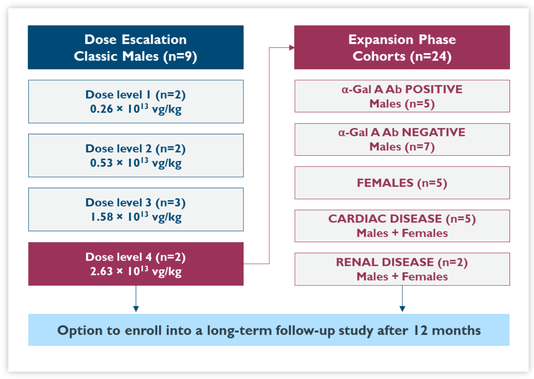
- Fabry disease is a progressive, multi-organ, lysosomal disease caused by pathogenic mutations in the GLA gene leading to deficiency of the lysosomal enzyme alpha-galactosidase A (α-Gal A) and accumulation of globotriaosylsphingosine (lyso-Gb3)
- Isaralgagene civaparvovec (ST-920) is an investigational 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 ERT infusions
  - Durable efficacy
  - Low immunogenicity
- STAAR is a Phase 1/2 open-label, multicenter study evaluating 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



Main Cardiac Objectives

- Cardiac function assessed by ECG and ECHO
- CMR by measuring LVEF, LV global Longitudinal strain, LV systolic function, and LVMI
- Cardiac functional biomarkers (Troponin T and N-Terminal ProB-type Natriuretic Peptide)
- Patient-reported outcomes and QoL scores

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 participant 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
Baseline Cardiac Symptoms (n):			
• Left ventricular hypertrophy	9	4	13
• Palpitations	10	2	12
• Tricuspid valve incompetence	6	1	7

- 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
- Cardiac AEs were mild in nature, with only one reported as Grade 3. The cardiac events observed reflect the underlying Fabry cardiomyopathy and conduction disease.
- LFT elevation events (all Grade 1 with one requiring short term corticosteroid) resolved without clinical sequalae
- No thrombocytopenia were observed. No AEs led to study discontinuation and there were no deaths.

ECG and ECHO: stability over 52 weeks

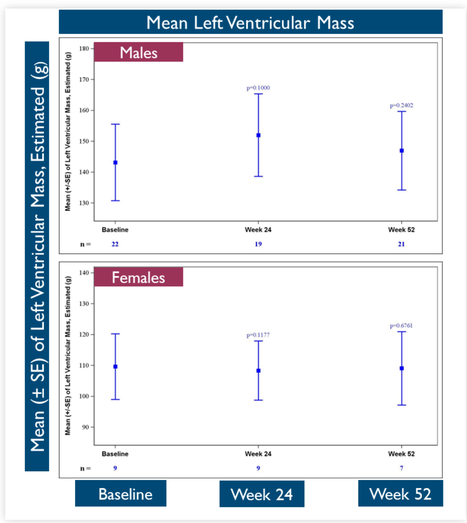
ECG	Baseline Mean ± SD (n)	Week 52 Mean Change from Baseline ± SD (n)
PR Interval (ms)	148.5 ± 24.41 (33)	5.5 ± 19.19 (32)
Ventricular Rate (beats/min)	65.8 ±11.02 (33)	-0.9 ± 11.65 (32)
QT Interval (ms)	401.0 ± 32.75 (33)	2.6 ± 31.71 (32)
QRS Interval (ms)	101.6 ± 17.44 (33)	1.5 ± 11.64 (32)
QTc Interval (ms)	414.6 ± 25.35 (33)	-1.7 ± 21.23 (32)
ECHO		
Ventricular Wall Thickness (mm)	15.71 ± 10.12 (29)	3.15 ± 9.23 (25)

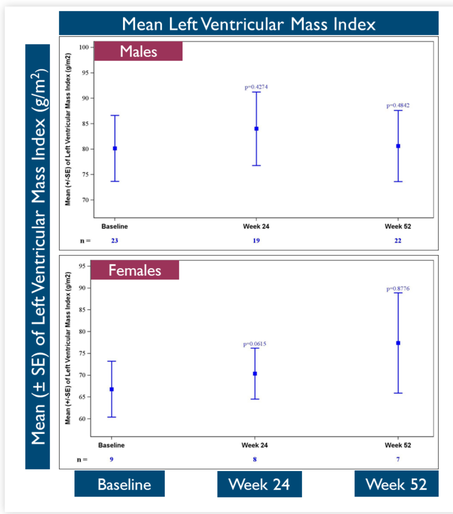
- Change in mean Ventricular Rate, and mean intervals of PR, QT, QRS, and QTc demonstrated cardiac stability
- Ventricular wall thickness (remained stable) and QTc Interval (slightly improved) are predictors of cardiac events and arrythmia
- Cardiac structure and function remained stable over 52 weeks

Myocardial Morphology Stability

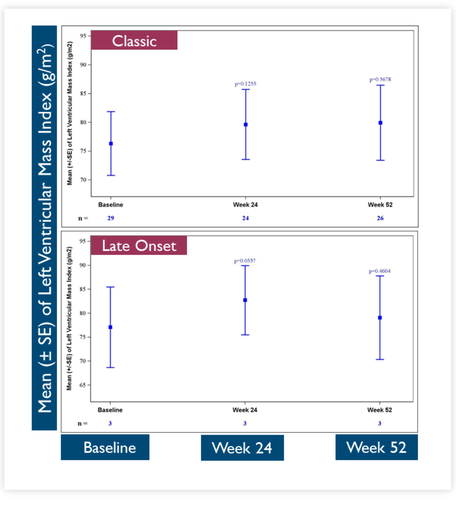
- Mean Left Ventricular Mass and Left Ventricular Mass Index were measured by Cardiac MRI for males and females, at baseline, 6 months, and 12 months
- At 1-year follow up, no statistically significant changes from baseline were seen within each of the following sub-groups: gender, classic/late-onset, and prior cardiac hypertrophy
- Overall stable myocardial morphology over time for at least 1-year irrespective of patient subgroup

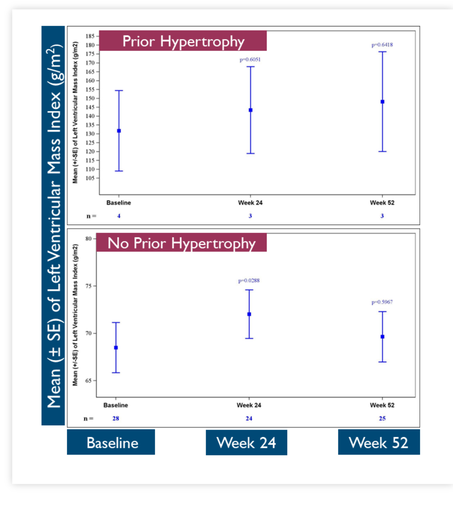
Males and females: Baseline, 6 and 12 months





Classic and late-onset disease type. No prior or prior hypertrophy. Baseline, 6 and 12 months





Maintained LV structure and function

Males and females: Baseline and week 52 (12 months)

	Females		Males	
	Baseline Mean ± SD (n)	Week 52 Mean Change from Baseline ± SD (n)	Baseline Mean± SD (n)	Week 52 Mean Change from Baseline ± SD (n)
End Systolic Volume (mL)	39.48 ± 11.04 (9)	4.2 ± 13.19 (7)	61.64 ± 17.56 (22)	-0.67 ± 18.18 (21)
LVEF (%)	68.32 ± 6.48 (9)	-2.4 ± 4.38 (7)	63.18 ± 6.38 ((23)	0.87 ± 6.81 (22)
LVGLMS (%)	-14.48 ± 3.1 (9)	-2.70 ± 3.16 (6)	-14.26 ± 3.67 (20)	0.72 ± 3.05 (17)

	Baseline Mean ± SD (n)	Week 52 Mean Change from Baseline (95% CI)
Troponin T (ng/L)	22.3 ± 29.69 (25)	1.0± 5.74 (24)
N-Terminal ProB-type Natriuretic Peptide (pg/ml)	277.8 ± 451.72 (20)	60.8 ± 136.14 (19)

- Overall, the ejection fraction and the global longitudinal strain remains was preserved over 52 weeks
- Stable Troponin T levels indicate stable myocardial disease over the time of the investigations
- Stable N-Terminal ProB-type Natriuretic Peptide levels indicates overall stable cardiorenal function throughout the time of study participation in related individuals

Disease severity and quality of life

QoL: SF-36 (52 weeks)

- Statistically significant and clinically meaningful improvements were observed in general health, physical component, bodily pain, role-physical, vitality, and social functioning scores

QoL: GSRS (52 weeks)

- Statistically significant improvements in GSRS score and diarrhea observed

FOS-MSSI (52 weeks)

- Age-adjusted score mean change (95% CI) from baseline at Week 52 -4.21 [-6.2, -2.2], p=0.0002
- Nine participants (five on ERT) improved their disease severity category (mild, moderate, severe) from baseline compared to last assessment
- 14 participants were mild both at baseline and at last assessment

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

- ST-920 gene therapy was well-tolerated with an **excellent safety profile**
- **Stable cardiac function** was observed over one and two years
- **Consistent cardiac structural stability** observed across clinical and demographic subgroups
- Clinically and statistically significant **Quality of Life improvements** were observed
- **Total and/or neutralizing α-Gal A antibodies decreased** markedly
- Our team intends to **complete submission of a BLA** for ST-920 in 2026

Acknowledgments

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Data cut-off date: 10 April 2025

Abbreviations: eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; ECG, electrocardiogram; ECHO, echocardiogram; CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction; LVGLS., Left ventricular global longitudinal strain ; LV, left ventricle; LVMI, left ventricular mass index; AE, adverse event; TESAE, treatment emergent serious adverse event; LFT, liver function test; MM, milli meter; N, number, M, male; F, female; g, grams; g/m^2, grams per meter squared; ml;, milli liter; ms, milli second; SF-36, 36-Item Short Form Health Survey; QoL:, quality of life; GSRS, gastrointestinal symptom rating scale; FOS-MSSI, fabry outcome survey; SE, standard error; SD, standard deviation.

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