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

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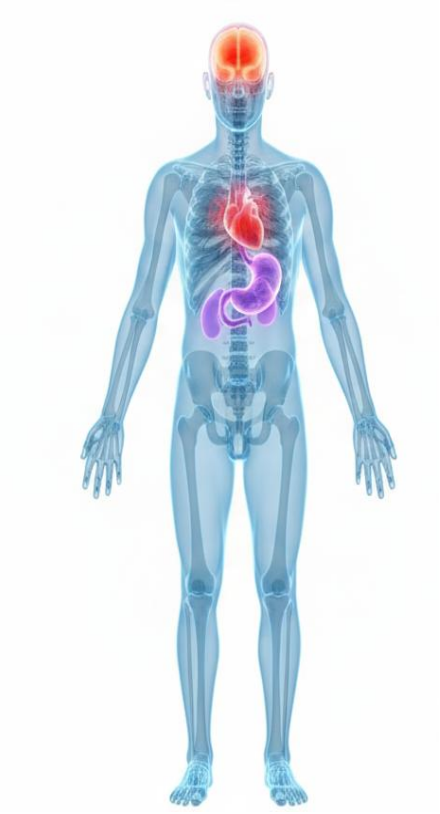
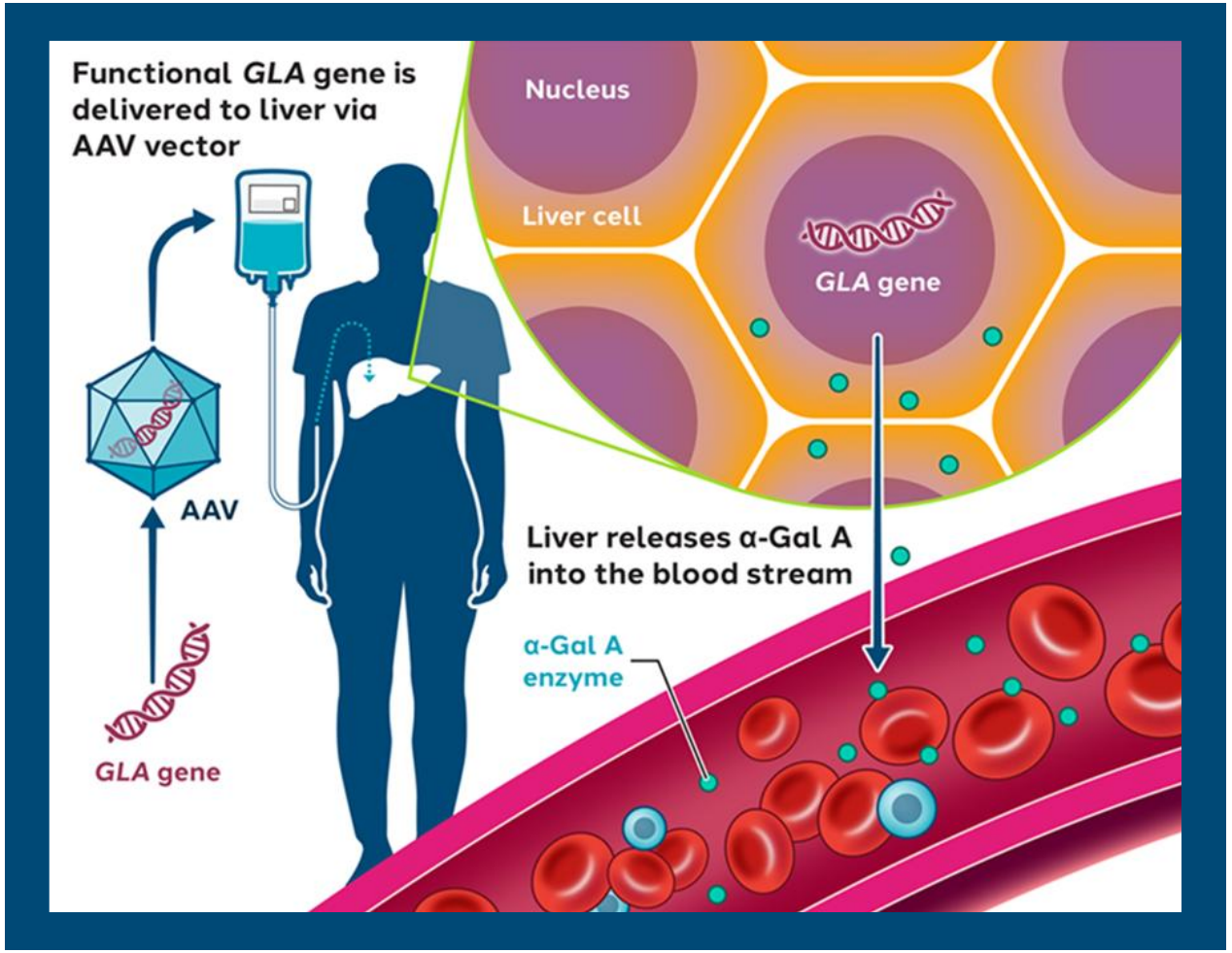
Fabry is a debilitating disorder causing serious damage to vital organs including cardiac dysfunction, not adequately addressed by current therapies



- **A lysosomal disease involving major organs including the heart**
  - Hypertrophic cardiomyopathy, myocardial infarction, arrhythmias, and diastolic heart failure
- **Reduces life expectancy** by ~20 years for males and 10-15 years for females
  - Cardiovascular disease is the most common cause of death (75%) in Fabry disease patients mainly due to heart failure and arrhythmia
- **Current standards of care are burdensome, bringing limited clinical benefits**
  - Lifelong, highly burdensome treatments
  - Poor patient compliance
  - Cardiac dysfunction and complications persist
  - Negative eGFR slope remains with all current standards of care

Image generated by Google Gemini; eGFR, estimated glomerular filtration rate. Baig S et al. Europace 2018;20:153–61; Waldek S et al. Genet Med 2009;11:790–796; Linhart A et al. Euro Heart J 2007; 10:1228-1235

ST-920 employs a recombinant AAV2/6 vector with human GLA cDNA for continuous, liver-specific α-Gal-A expression



Advantages

- Convenient one-time administration
- Potential to eliminate ERT infusions
- Consistent plasma levels of endogenous α-Gal A
- Durable efficacy
- Low immunogenicity
- No prophylaxis with steroids or other immunomodulating agents required
- Potential to address unmet medical need including cardiac manifestations of Fabry

α-Gal A, alpha galactosidase A; AAV, adeno-associated virus; ERT, enzyme replacement therapy; GLA, galactosidase alpha; cDNA, copy DNA

STAAR Phase 1/2 clinical study overview

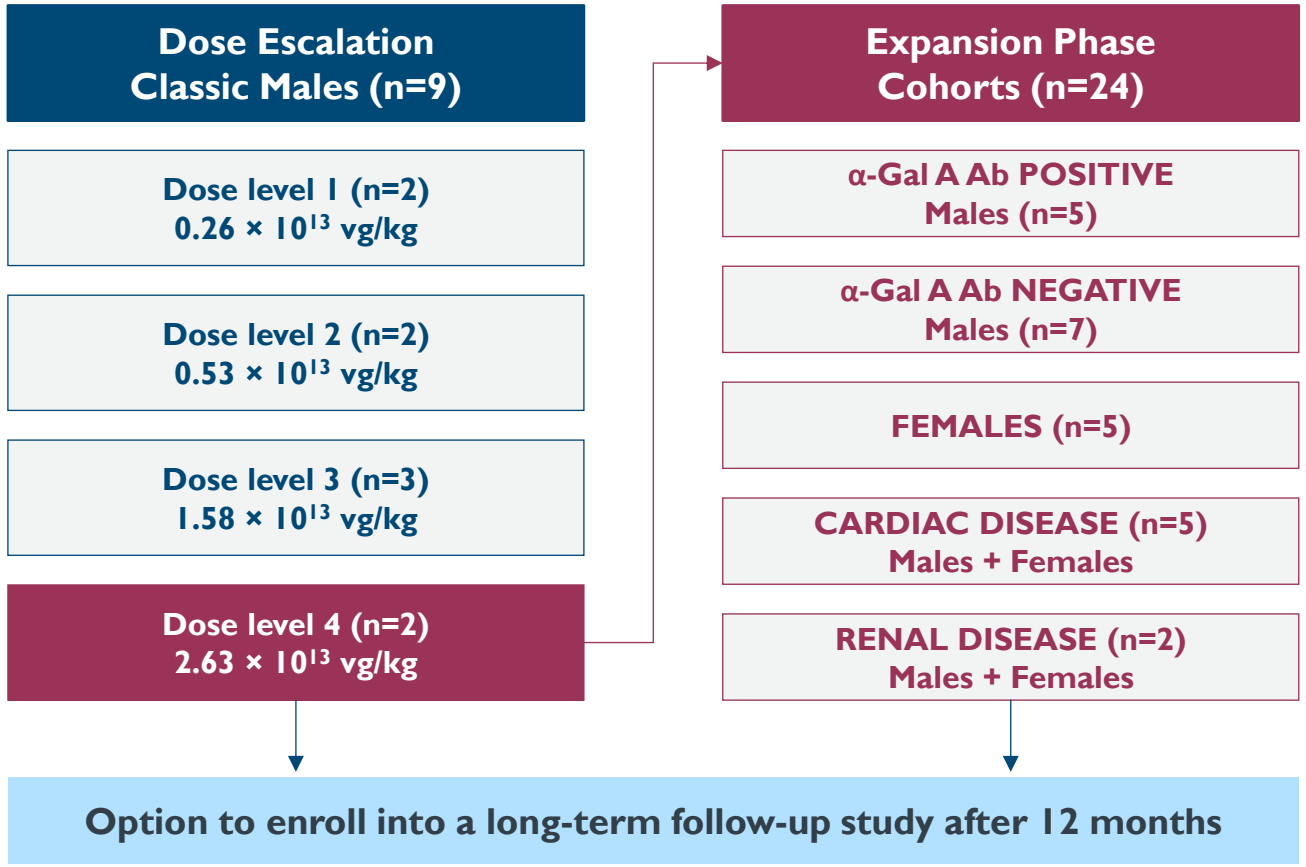
Global, multicenter, open-label, single dose, dose ranging study (ST-920-201, NCT04046224): Completed

Eligibility

- 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
- For cardiac cohort: Wall thickness ≥ 12mm or presentation with cardiac changes

Main Cardiac Objectives

- Cardiac function assessed by ECG, ECHO, and 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



α-Gal A, alpha galactosidase A; Ab, antibody; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; QoL, quality of life; vg/kg, vector genomes per kilogram of total body weight (as assessed by digital droplet PCR [ddPCR]); ECG, electrocardiogram; ECHO, echocardiogram; CMR, cardiac magnetic resonance; LVEF; left ventricular ejection fraction; LV, left ventricular; LVMI, left ventricular mass index; MM, millimeter; N; number

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

Data cut-off date: 10 April 2025
eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); ERT, enzyme replacement therapy; N, number, M, male; F, female

- Longest treated participant has achieved 4.5 years follow-up as of the April 2025 data cut-off
- Median duration of follow-up: 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

ST-920 showed a favorable safety profile

Summary of treatment-emergent AEs in ≥10% of 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	10 (30.3%)	0
Fatigue	9 (27.3%)	0
Nausea	9 (27.3%)	0
Diarrhea	6 (18.2%)	0
Paresthesia	5 (15.2%)	0
Myalgia	5 (15.2%)	1 (3.0%) (G3)
Dizziness	5 (15.2%)	0
Cough	5 (15.2%)	0
Abdominal Pain	4 (12.1%)	0
Palpitations	4 (12.1%)	0
Hypotension	4 (12.1%)	0
Infusion Related Reaction	4 (12.1%)	0
Urinary Tract Infection	4 (12.1%)	0
Dyspnoea	4 (12.1%)	0

Data cut-off date: 10 April 2025

AE, adverse event; LFT, liver function test; TESAE, treatment-emergent serious adverse event; SAE, serious adverse event; TMA, thrombotic microangiopathy; N, number; G, grade

- ST-920 was generally well-tolerated with majority of AEs being Grade 1-2 in nature
- LFT elevation events have been Grade 1 (only one requiring short term corticosteroid); all resolved without clinical sequalae
- TESAEs were reported in 4 participants, all Grades 2 or 3:
  - Left arm pain, non-cardiac chest pain, sepsis, stroke, shoulder enthesopathy (only related SAE reported)
- 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
- No thrombocytopenia observed
- No AEs led to study discontinuation
- No deaths

ECG and ECHO findings demonstrate stability over 52 weeks

ECG	Baseline Mean ± SD (n)	Week 52 Mean Change from Baseline ± SD (n)
PR Interval	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)

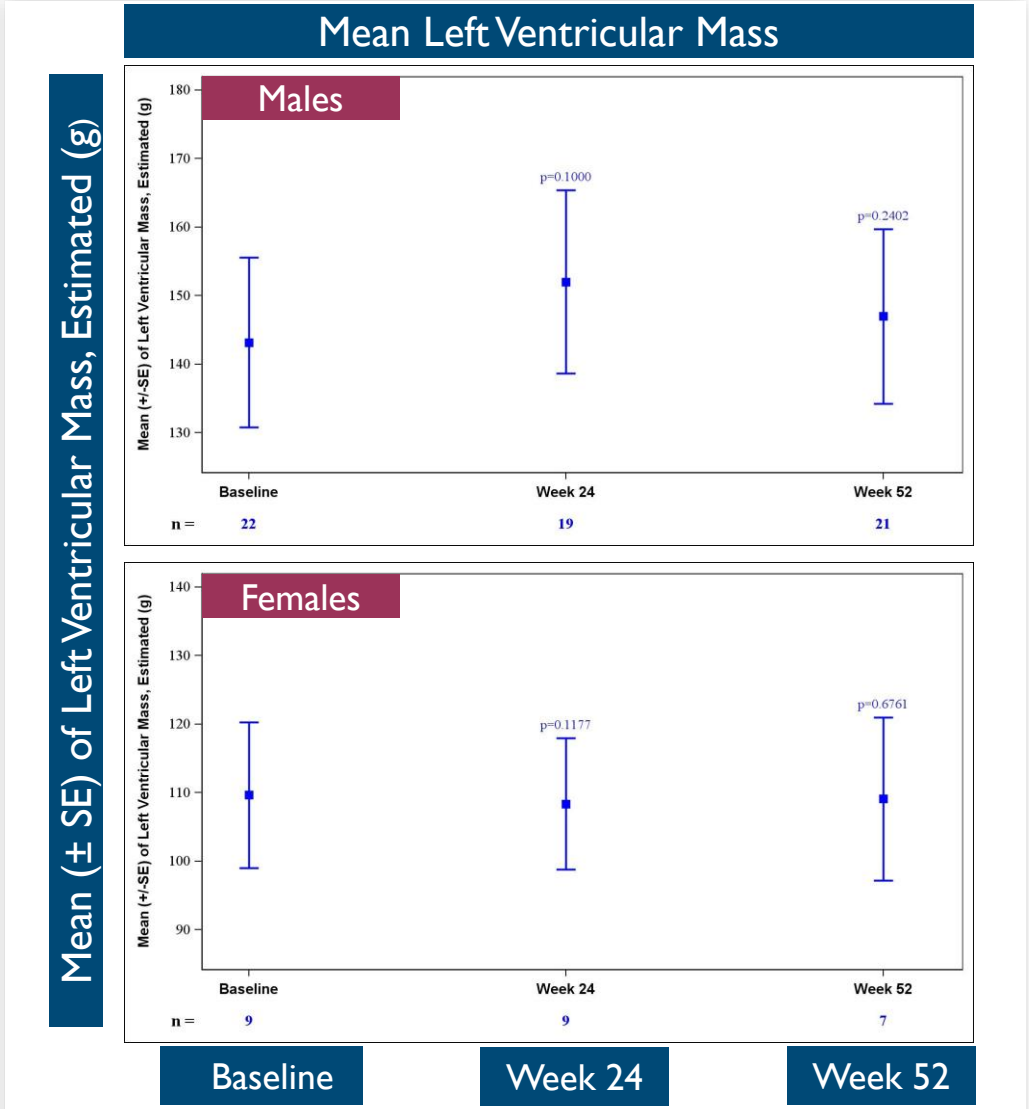
ECHO	Baseline Mean ± SD (n)	Week 52 Mean Change from Baseline ± SD (n)
Ventricular Wall Thickness (mm)	15.71 ± 10.12 (29)	3.15 ± 9.23 (25)

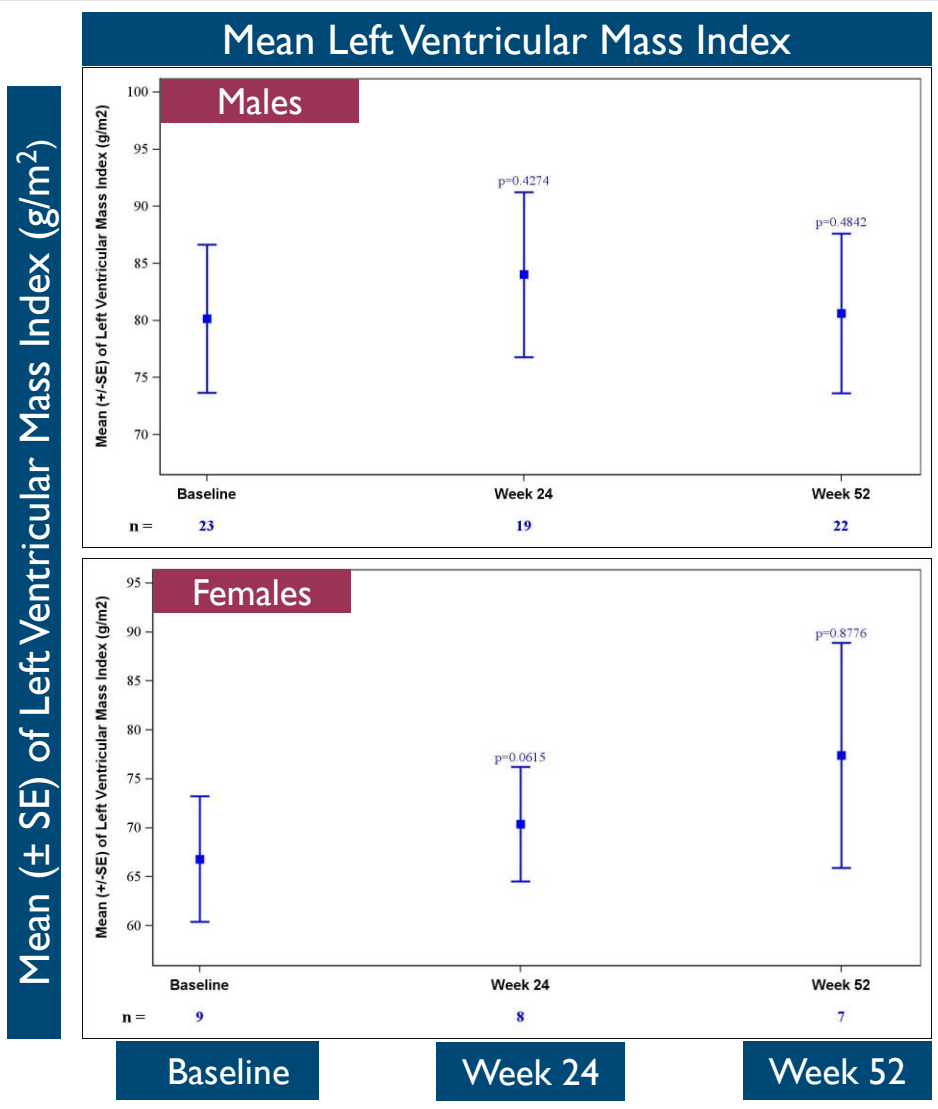
- Mean PR interval, Mean Ventricular Rate, QRS (ms), Baseline QT (ms), Baseline QTc mean interval (ms), LVMI and EF indicate clinical stability across the various subgroups
- Ventricular wall thickness and QTc Interval are predictors of cardiac events and arrythmia
- QTc interval slightly improved and ventricular wall thickness remained stable
- Cardiac structure and function remained stable over 52 weeks

Data cut-off date: 10Apr2025

EF, ejection fraction; LVMI, left ventricular mass index; QRS, Q wave R wave S wave interval; QT, Q wave T wave interval; QTc, rate-corrected QT interval; PR, P wave to R wave interval; ECG, electrocardiogram; N, number; MM, millimeter; MS, milli second; SD, standard deviation; * p-value > 0.05 for all parameters above

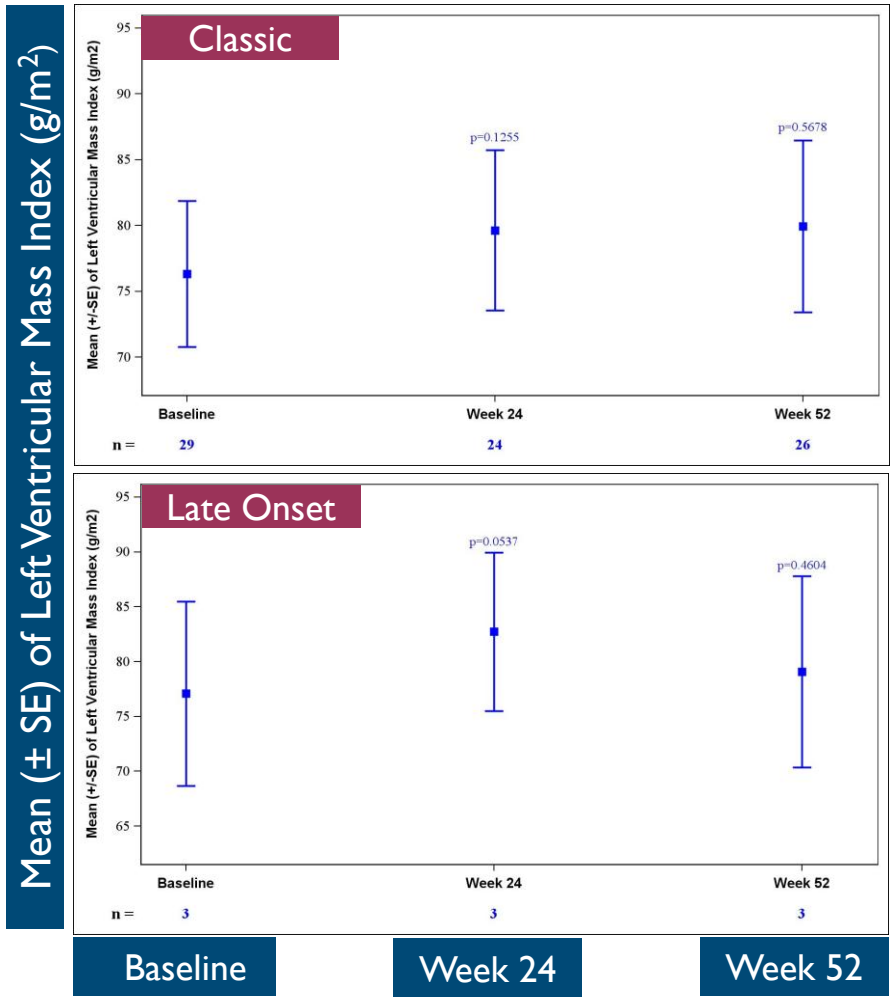
Cardiac MRI demonstrates stability of myocardial morphology in males and females at 6 and 12 months

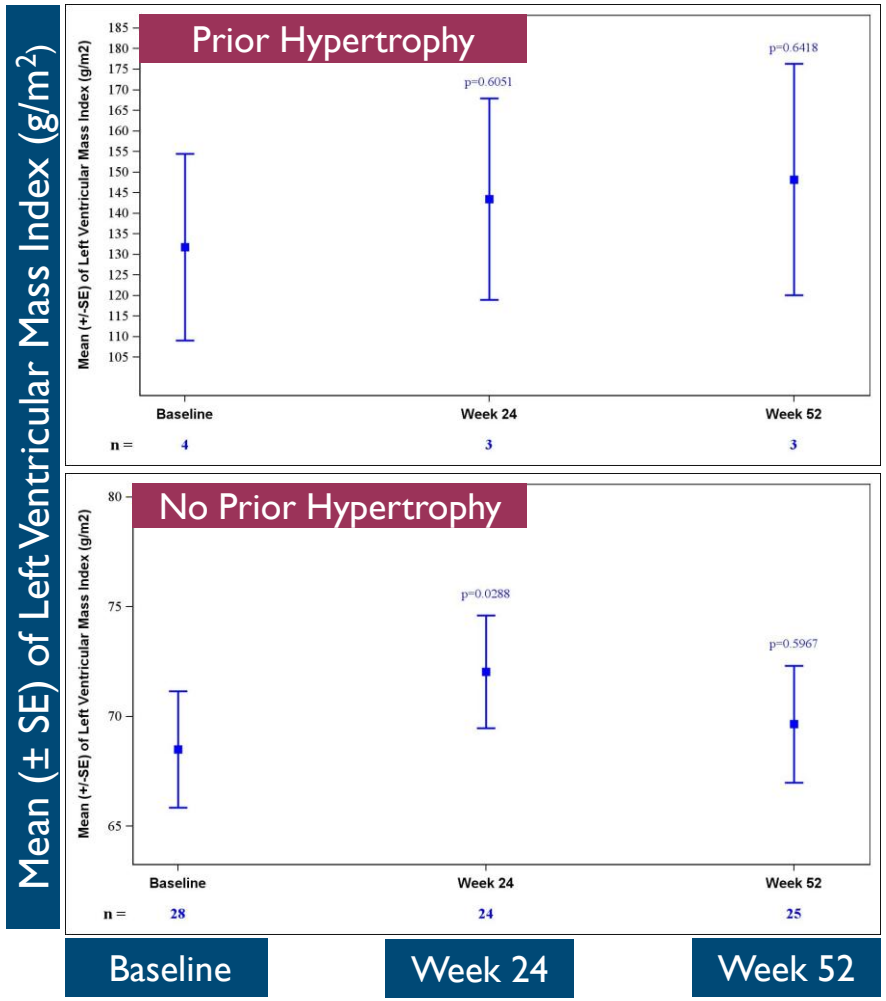




Data cut-off date: 10Apr2025
Analysis of ST-920 treated subjects at 24 weeks and 52 weeks compared to their baseline; N, number; G, grams

Consistent cardiac structural stability across clinical and demographic subgroup





Data cut-off date: 10Apr2025
Analysis of ST-920 treated subjects at 52 weeks; N, number; G/M^2, grams per meter square; G, grams

Cardiac MRI demonstrates preservation of left ventricular structure and systolic function

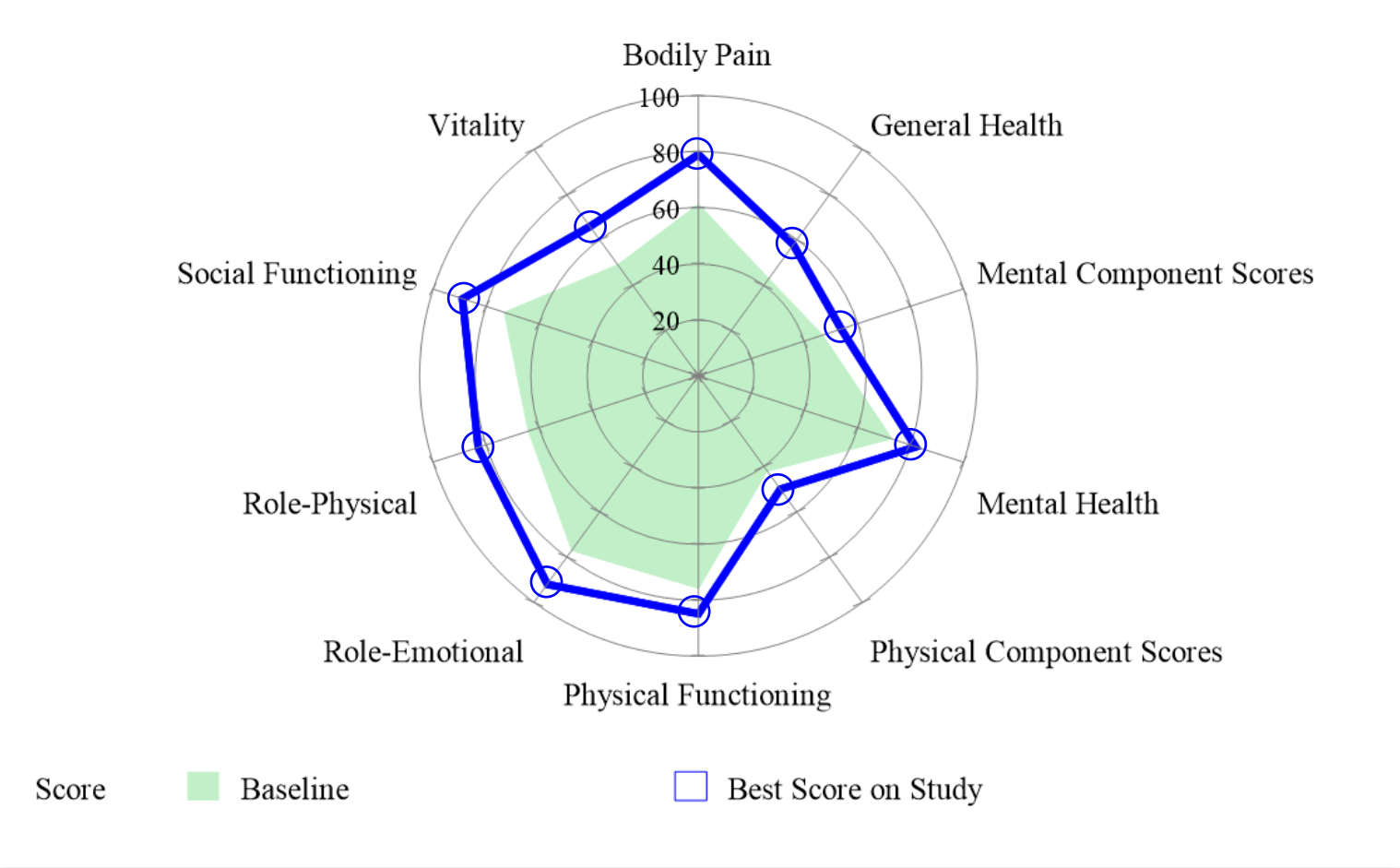
	Females		Males	
	Baseline Mean ± SD (n)	Week 52 Mean Change from Baseline ± SD (n)	Baseline Mean± SD (n)	Week 52 Mean Change from Baseline ± SD (n)
End Systolic Volume (mL)	39.48 ± 11.04 (9)	4.2 ± 13.19 (7)	61.64 ± 17.56 (22)	-0.67 ± 18.18 (21)
LVEF (%)	68.32 ± 6.48 (9)	-2.4 ± 4.38 (7)	63.18 ± 6.38 ((23)	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)

Data cut-off date: 10Apr2025
LVEF, left ventricular ejection fraction; LVGLMS, left ventricular global longitudinal myocardial strain; N, number; MRI, magnetic resonance imaging; ML, milli liter;NG/L, nanogram per liter; PG/ML, picogram per milliliter; CI, confidence interval

- Overall, the ejection fraction and the global longitudinal strain remains 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

Significant improvements observed in all SF-36 scores including bodily pain and physical role



FOS-MSSI:

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

SF-36 (52 weeks):

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

GSRS (GI Symptom Rating Scale)

- Statistically significant improvement in GSRS score and diarrhea at 52 weeks compared to baseline

Data cut-off date: 10Apr2025
Analysis of ST-920 treated subjects with ≥12 m follow-up (n=32). "Month 12" is Week 52 study timepoint. All p-values are unadjusted nominal p-values. FOS-MSSI, Fabry outcome survey-mains severity score; SF-36. 36-item short form health survey; GI, gastrointestinal. Best score from up to 4.5 years follow up data.

Summary

- **Totality of data supports 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 in this population of adults with symptomatic Fabry disease:
  - Mainly Grade 1 and 2 Adverse Events, no discontinuation based on ST-920
  - No prophylactic steroids or other immunomodulatory agents administered
  - Cardiac adverse events were mild in nature, with only one reported as Grade 3
- **Stable cardiac function** was observed over one year.
- **Consistent Cardiac Structural Stability** across clinical & demographic subgroups over one year of follow up
- **Stable Cardiac Biomarkers** over 1 year
- **Clinically meaningful improvement** in Patient Reported Outcomes (Bodily Pain, Physical Functioning & Role-Physical)
- **ST-920 has potential as a one-time, durable treatment option for Fabry disease that can improve patient outcomes**
- Our team intends to complete submission of a **BLA for ST-920 in 2026 under the Accelerated Approval pathway**

Data cut-off date: 10Apr2025

Acknowledgments

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