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

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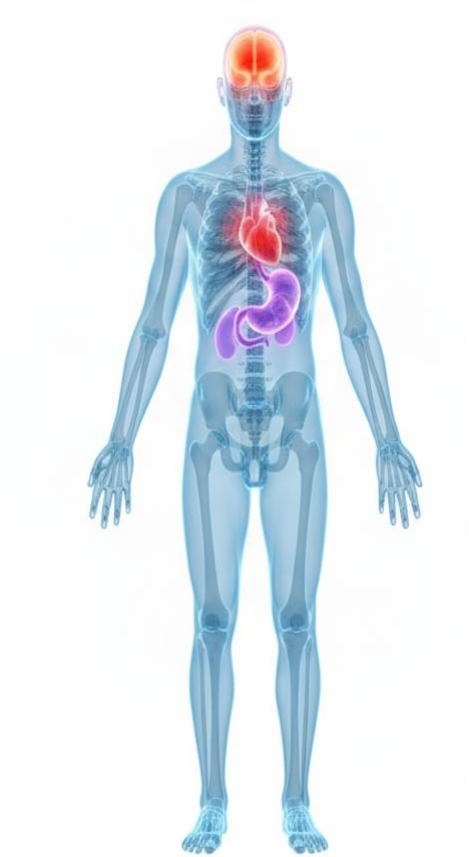
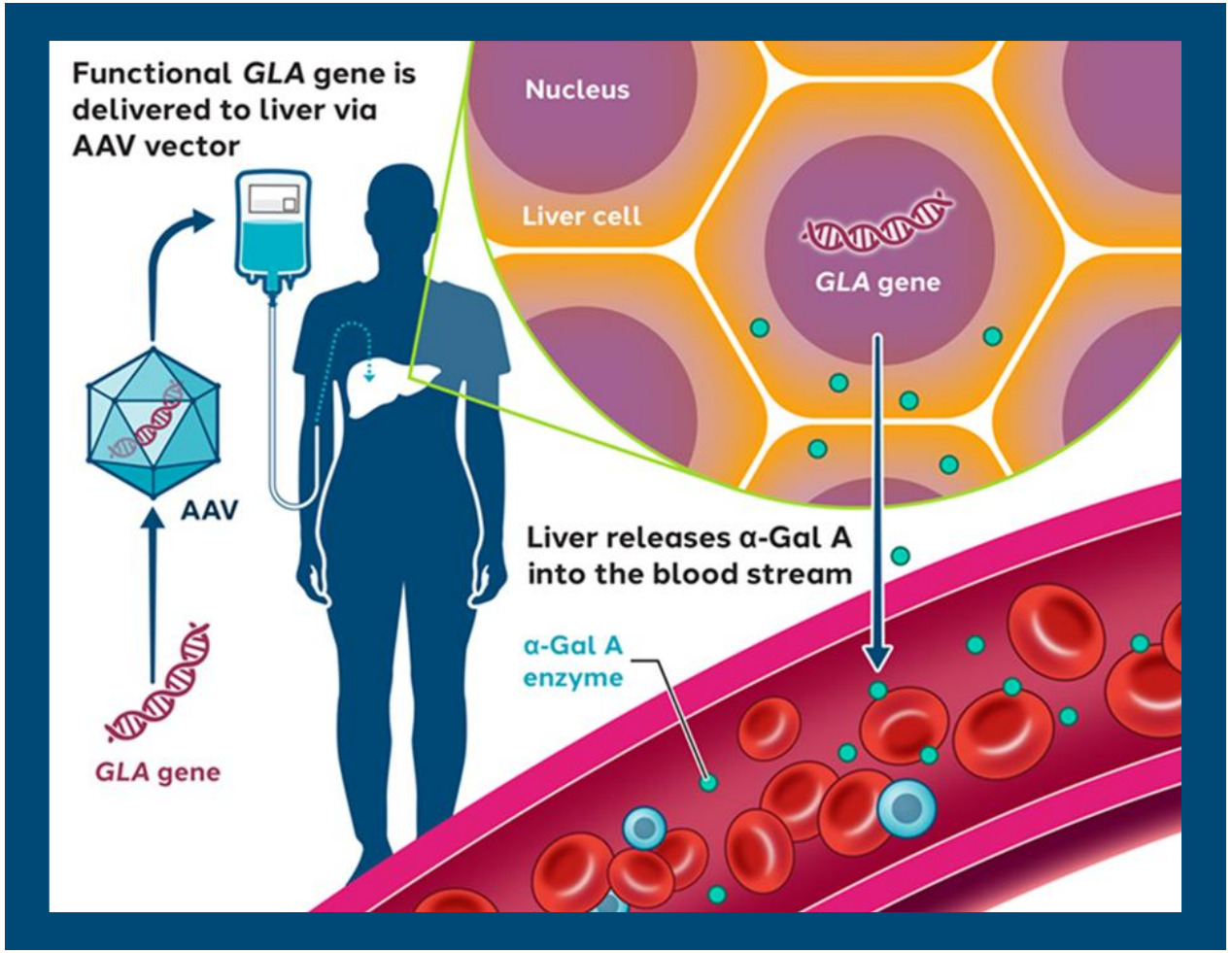
Fabry disease is a debilitating disorder causing serious damage to vital organs, leading to serious complications and premature death



- **A lysosomal disease involving major organs**
  - **Kidney:** progressive kidney damage leading to kidney failure
  - **Cardiac:** heart enlargement, irregular heartbeat, heart attack
  - **Neurological:** blood vessel damage that can lead to stroke, dizziness, headaches
  - **Gastrointestinal:** abdominal pain, diarrhea and nausea
  - **Other:** skin and nerve damage, inability to sweat, chronic pain and fatigue
- **Reduces life expectancy** by ~20 years for males and 10-15 years for females
- **Current standards of care are burdensome, bringing limited clinical benefits**
  - Lifelong, highly burdensome treatments
  - Poor patient compliance
  - Renal dysfunction, cardiac complications and cerebrovascular issues persist
  - Negative eGFR slope remains with all current standards of care

Image generated by Google Gemini; eGFR, estimated glomerular filtration rate

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

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

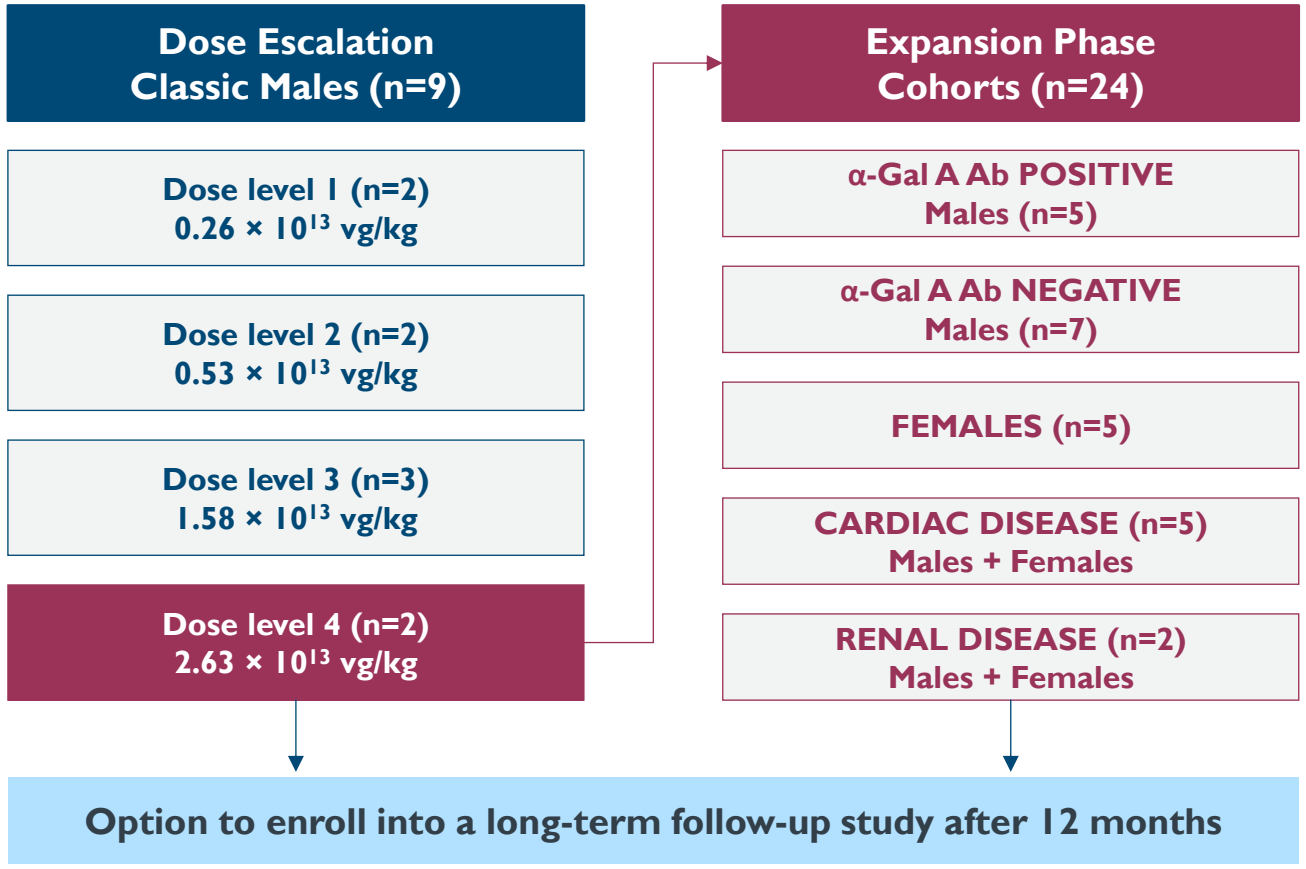
Global, multicenter, open-label, single dose, dose ranging study (ST-920-201, NCT04046224): Completed

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

Main Objectives

- Safety and tolerability of ST-920
- 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



α-Gal A, alpha galactosidase A; AAV, adeno-associated virus; 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]), 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
$eGFR_{CKD-EPI}$ 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 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

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

ST-920 showed a favorable safety profile

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

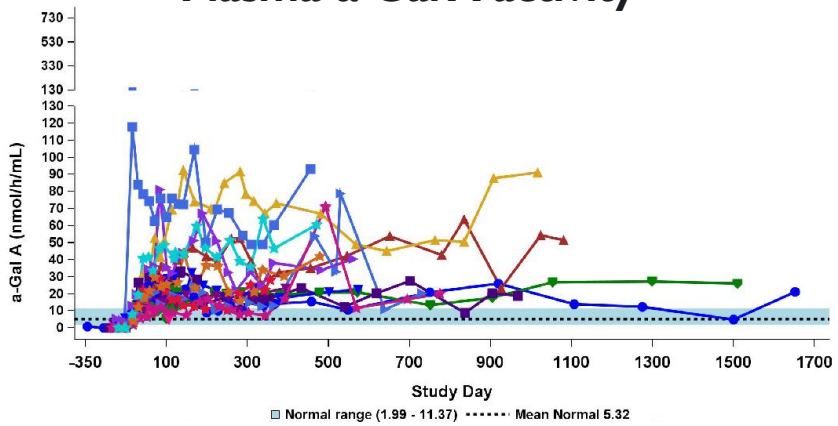
AE by preferred term	Treated subjects (n=33)	
	All grades	Grade 3-4
Pyrexia	20 (60.6%)	1 (3.0%) (G3)
COVID-19	12 (36.4%)	0
Nasopharyngitis	11 (33.3%)	0
Headache	10 (30.3%)	0
Fatigue	9 (27.3%)	0
Nausea	9 (27.3%)	0
Diarrhea	6 (18.2%)	0
Paresthesia	5 (15.2%)	0
Myalgia	5 (15.2%)	1 (3.0%) (G3)
Dizziness	5 (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

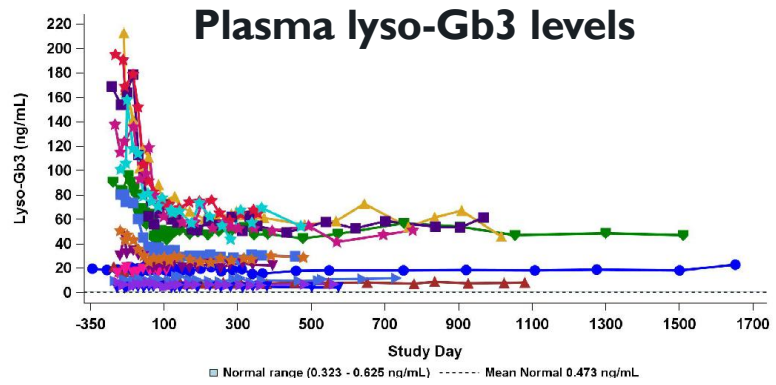
Data cut-off date: 10 April 2025

AE, adverse event; LFT, liver function test; TESAE, treatment-emergent serious adverse event; SAE, Serious Adverse Event; TMA, Thrombotic Microangiopathy

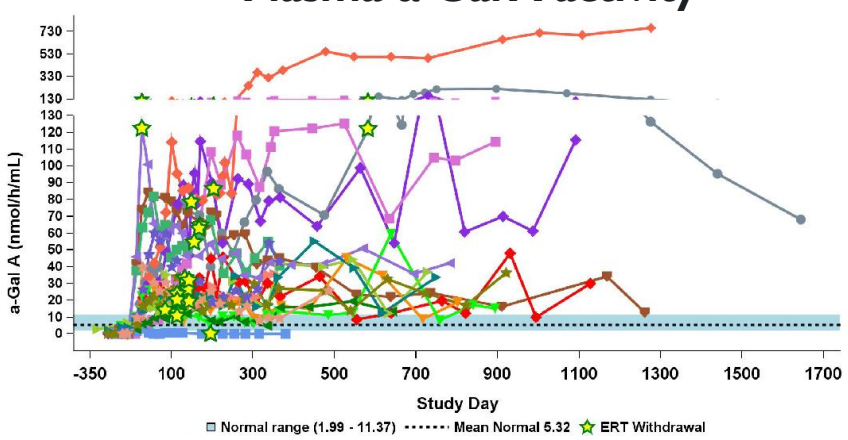
- ST-920 was generally well-tolerated with majority of AEs being Grade 1-2 in nature
- LFT elevation events have been Grade 1(only one requiring short term corticosteroid); all resolved without clinical sequalae
- TESAEs were reported in four participants, all Grades 2 or 3:
  - Left arm pain, non-cardiac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

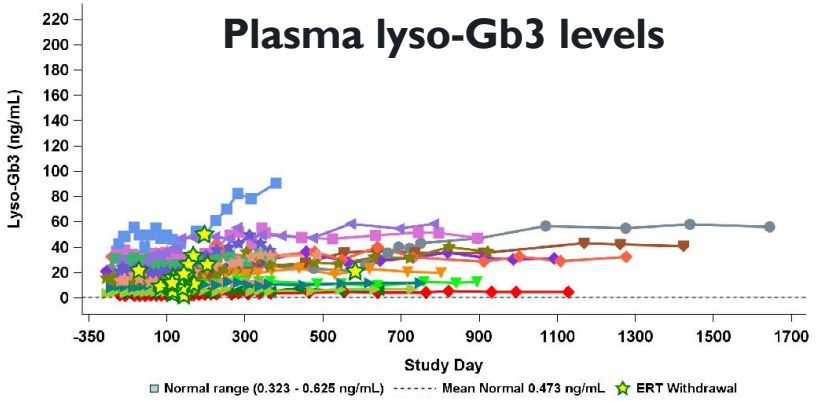
Durable plasma α-Gal A activity with lyso-Gb3 reduction and stability in naïve or pseudo-naïve and ERT-experienced participants





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





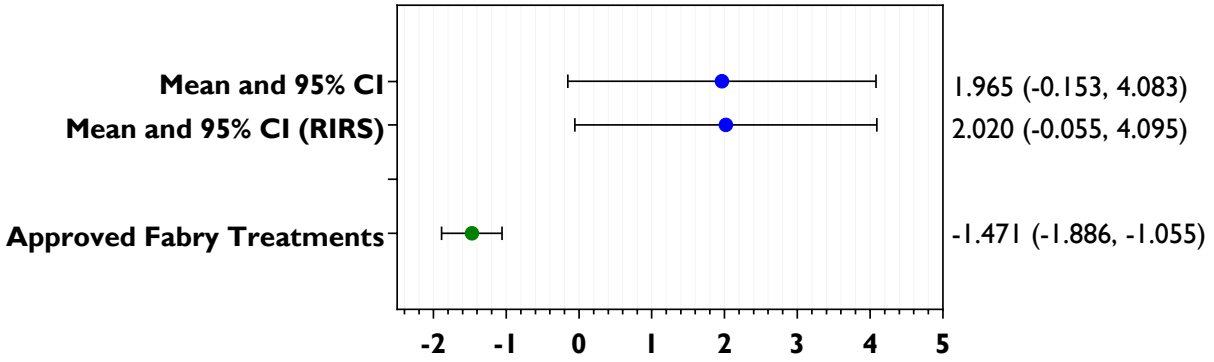
ERT participants (n=18) of which 17 have sustained elevated levels of plasma α-Gal A and stable levels of lyso-Gb3 following ERT withdrawal

Data cut-off date: 10 April 2025
α-Gal A activity measured using 3-hour reaction time. Normal range determined in healthy males and females. Long Term Follow-up Data: Data points > Study Day 365.
α-Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; N, number

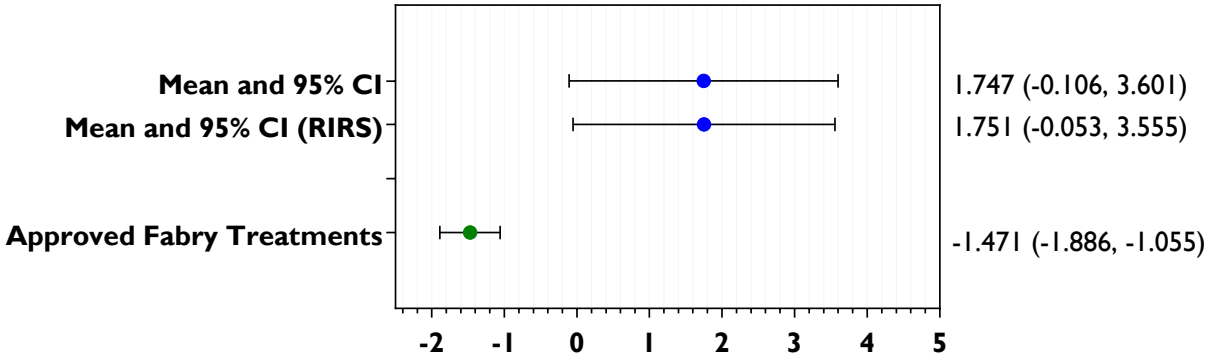
Positive mean annualized eGFR slope observed at 52 weeks

- Improvements in renal function observed across all 32 participants at 52 weeks and 19 participants at 104 weeks
- Supportive mean annualized eGFR slopes observed across subgroups, demonstrating consistency in effect across participants

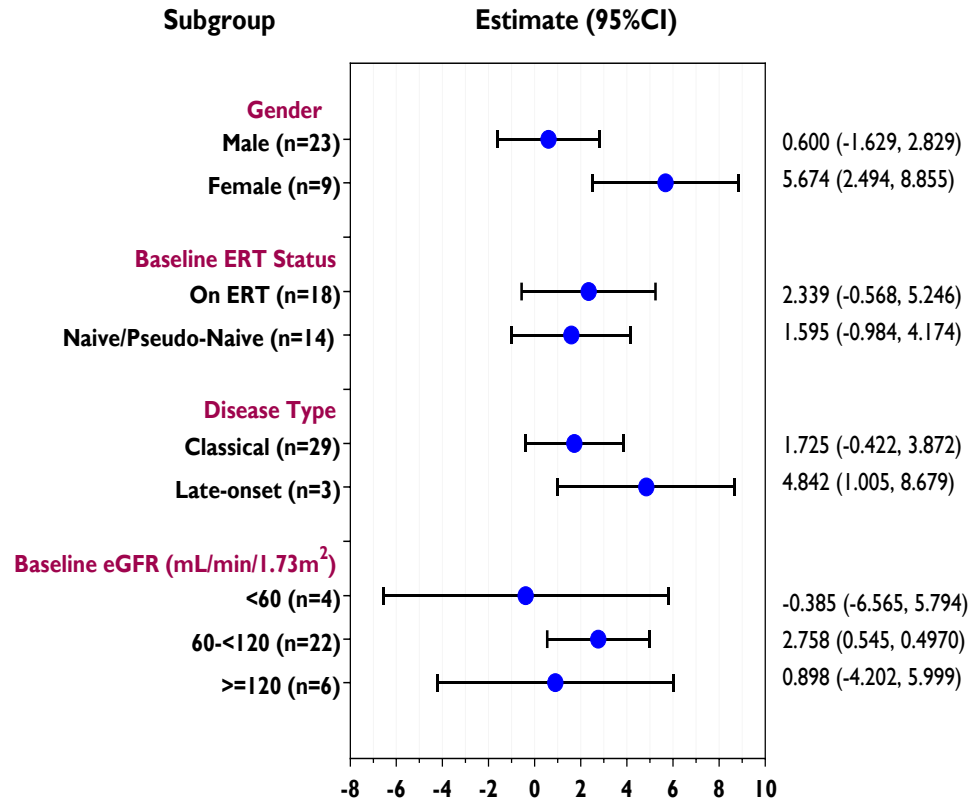
eGFR slope at **52** weeks (n=32)



eGFR slope at **104** weeks (n=19)



eGFR slope at **52** weeks (n=32): Subgroups

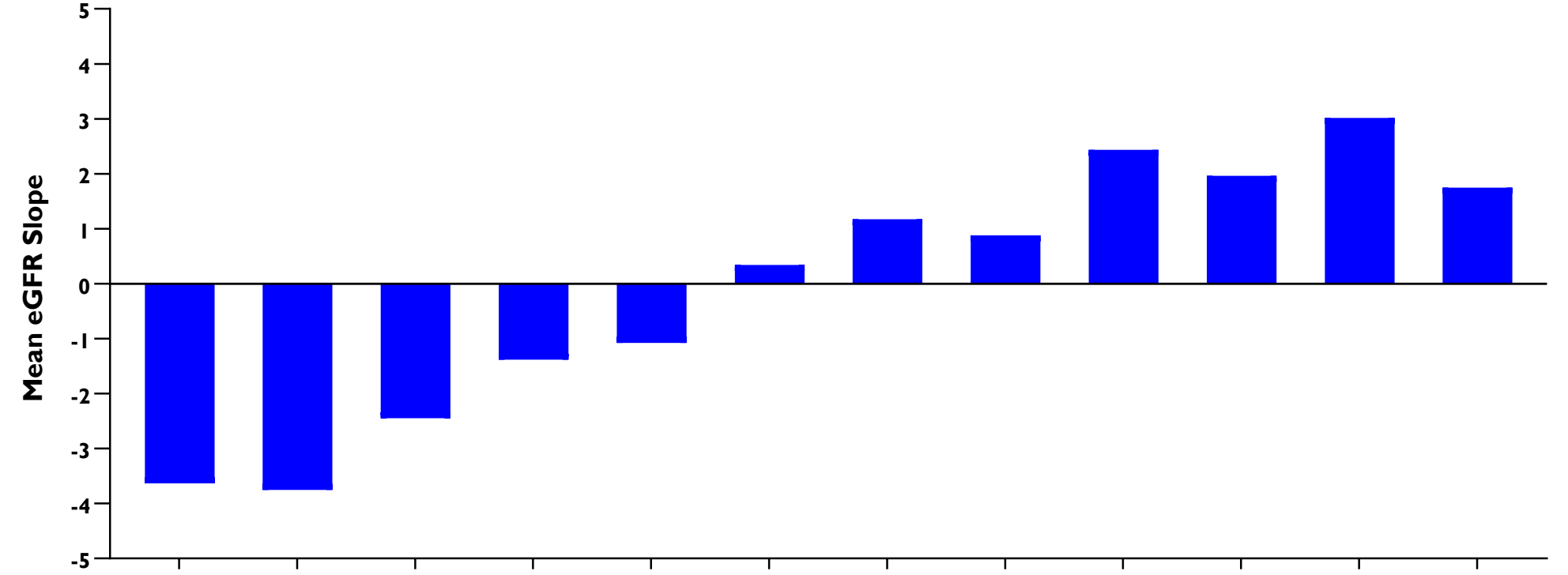


Data cut-off date: 10 April 2025

*A meta-analysis of publications of approved Fabry treatments (Fabrazyme, Galafold, Replagal) was conducted (Feriozzi 2012, Hughes 2016). The mean and 95% CI were calculated with adjustments to age, gender, and baseline eGFR. The upper confidence limit (UCL) of the 95% CI, -1.055 mL/min/1.73m2/year, was used to rule out variability in data and serves as a conservative historical comparator for Fabry patients treated with approved therapies. One participant discontinued the study with 12 weeks eGFR data, thus not included in the analysis.

eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; CI, confidence interval; RIRS, a linear mixed model with random intercept random slope; UCL, upper confidence limit; N, number.

Sustained renal function improvement demonstrated over 24 months, with improvement seen as early as 24 weeks post ST-920 administration



	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	18m	24m
n	32	32	32	32	32	32	32	32	32	32	22	19
Mean	-3.634	-3.753	-2.445	-1.383	-1.075	0.340	1.17	0.881	2.433	1.965	3.016	1.747
Standard Deviation	23.5271	16.0491	12.8020	9.1339	8.7466	7.9199	6.2008	5.7350	5.9844	5.8738	4.5632	3.8453

Data cut-off date: 10 April 2025
eGFR; estimated glomerular filtration rate; N, number; M, months

Cardiac endpoints showed stability over an extended period

- Cardiac markers were generally stable for all participants, some with up to 4 years of data:
  - End-diastolic and end-systolic volume
  - LVM, LVMI and Left ventricular myocardial GLS
- T1 and T2 mapping remained stable for one year, and in six of the seven participants at two years
- MRI: EF% stable over one year in all participants (trend of increase in 50% who have reached week 104)
- Troponin (ng/L) and Pro-B-type Natriuretic Peptide (pg/ml) levels stable for all participants except one

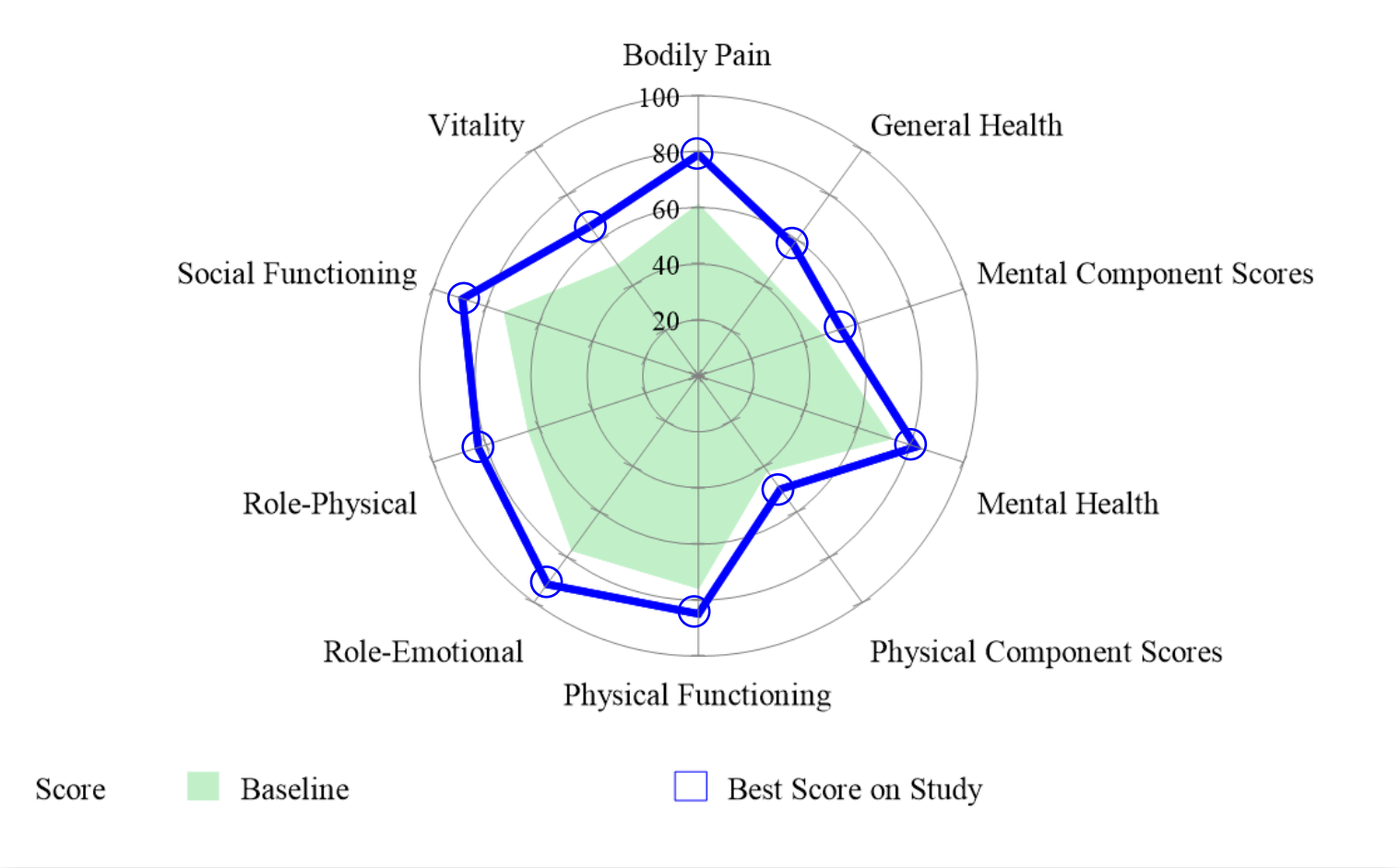
Friday, February 6

ST-920 cardiac-focused presentation by Dr. Rob Hopkin

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

Data cut-off date: 10 April 2025 (n=33)
LVM, Left Ventricular Mass: LVMI, Left Ventricular Mass Index; GLS, Global Longitudinal Strain; EF%, Left ventricular Ejection Fraction (percent); MRI, magnetic resonance imaging

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.

Reduction or elimination of antibodies against α-Gal A

	Anti-α-Gal A Total Antibodies (TAb) Titer		Anti-α-Gal A Neutralizing Antibodies (NAb) Titer	
	Baseline	On-study	Baseline	On-study
Participant 1	1280	Undetectable (M24)	160	Undetectable (W36)
Participant 3	160	Undetectable (W24)	Undetectable	Undetectable
Participant 4	160	Undetectable (W52)	Undetectable	Undetectable
Participant 5	10240	Undetectable (M36)	320	Undetectable (M36)
Participant 10	80	Undetectable (W4)	10	Undetectable (W4)
Participant 13	5120	160 (M24)	160	10 (M24)
Participant 16	2560	Undetectable (M24)	40	Undetectable (W52)
Participant 25	160	Undetectable (W4)	160	Undetectable (W4)
Participant 31	80	Undetectable (W12)	10	Undetectable (W4)
Participant 32	20480	10240 (W52)	640	640 (W52)

Data cut-off date: 10Apr2025
α-Gal A, alpha-galactosidase A; TAb, total antibody; NAb, neutralizing antibody; W, week

- 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

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 above current standards of care**
- ST-920 gene therapy was well-tolerated with an **excellent safety profile**
- **A positive mean annualized eGFR slope was** observed in 32 participants with 52-weeks of follow-up and 19 participants with 104-weeks follow-up, indicating improvements in renal function
- **Durable efficacy** was demonstrated with elevated expression of α-Gal A activity observed up to 4.5 years for the longest treated participant
- All 18 participants who began the study on ERT had been **withdrawn 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 in nine (90%) participants and were undetectable in eight (80%) out of 10 antibody positive participants
- **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

Investigators:

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