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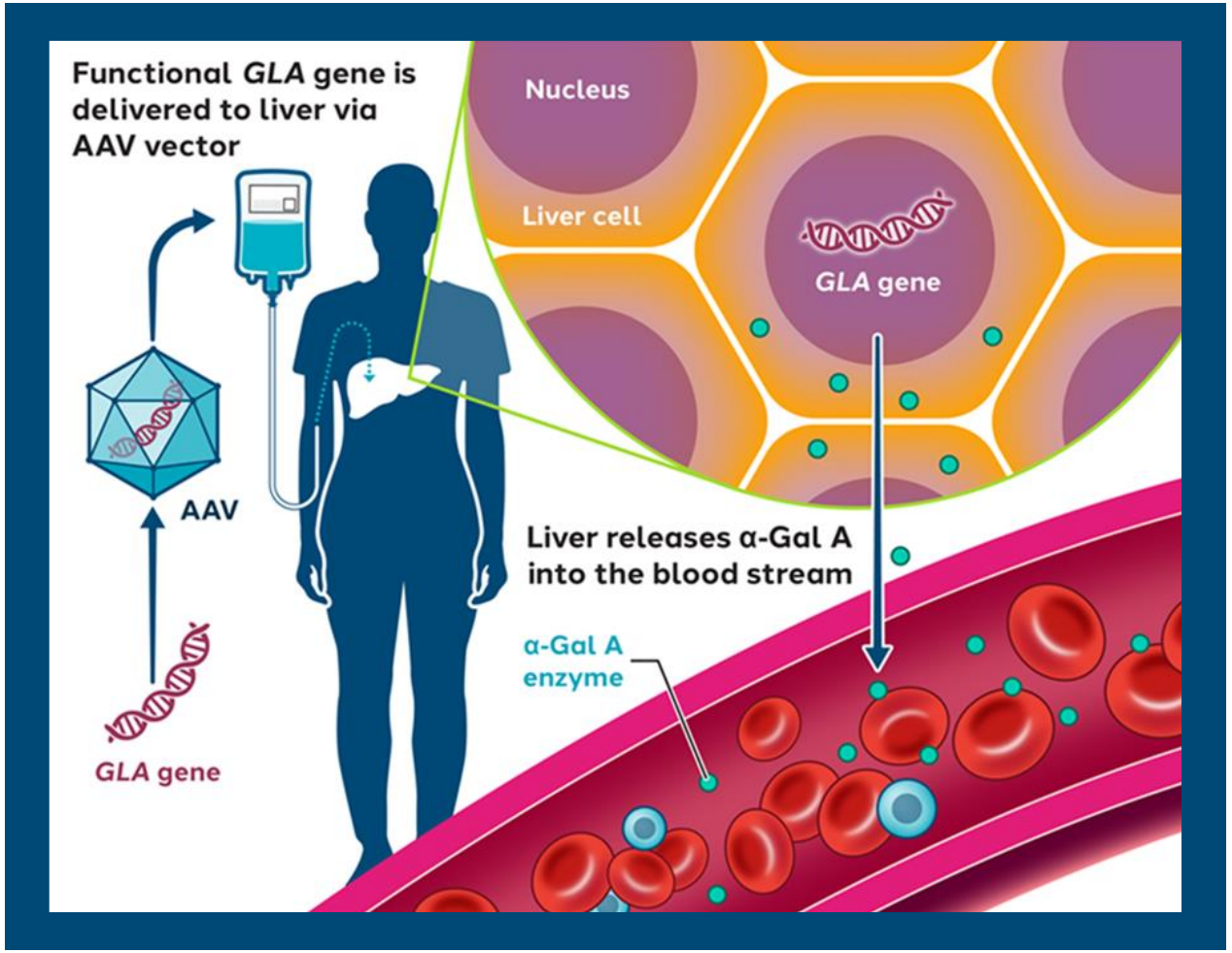
ST-920 employs a recombinant AAV2/6 vector with human GLA cDNA for continuous, liver-specific α-Gal-A expression



Advantages

- Convenient one-time administration
- Potential to eliminate ERT infusions
- 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.

STAAR Phase 1/2 clinical study overview

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

Eligibility

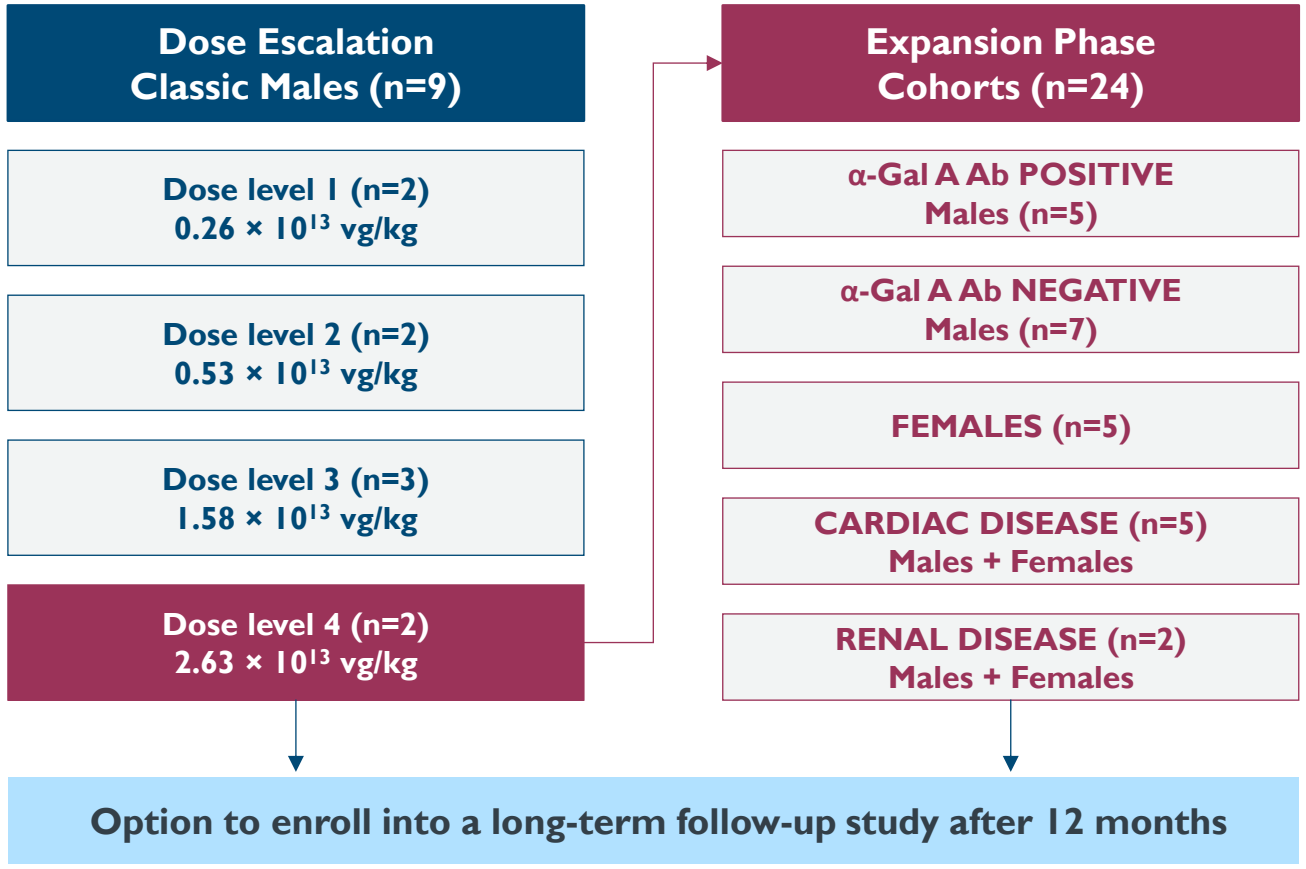
- Age ≥18 with symptomatic Fabry disease
  - ERT-naïve or pseudo-naïve (no ERT in prior 6 months)
  - On ERT
- eGFR ≥40 mL/min/1.73m^2
- No neutralizing antibodies to AAV6

Primary objective

- Safety and tolerability of ST-920

Other objectives - Evaluate

- 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; vg/kg, vector genomes per kilogram of total body weight (as assessed by digital droplet PCR [ddPCR])

Baseline characteristics: Dose escalation and dose expansion phases

	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 (22%)	7 (29%)	9 (27%)
• Pseudo-naïve	2 (22%)	4 (17%)	6 (18%)
• On ERT	5 (56%)	13 (54%)	18 (55%)
Baseline Fabry symptoms (n,%):			
• Cornea verticillata	4 (44%)	15 (63%)	20 (61%)
• Paresthesia	3 (33%)	7 (29%)	10 (30%)
• Anhidrosis	1 (11%)	5 (21%)	6 (18%)
• Angiokeratoma	2 (22%)	9 (38%)	11 (33%)
$eGFR_{CKD-EPI}$ category, n (%):			
• >90 ml/min/1.73 m^2	4 (44%)	15 (63%)	19 (58%)
• 60-90 ml/min/1.73 m^2	4 (44%)	6 (25%)	10 (30%)
• 40-<60 ml/min/1.73 m^2	1 (11%)	3 (13%)	4 (12%)

Data cut-off date: 12 September 2024
eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); ERT, enzyme replacement therapy; N, number, M, male; F, female

ST-920 is generally well tolerated with a favorable safety profile

Summary of treatment-emergent AEs in >3 subjects of 33 subjects treated

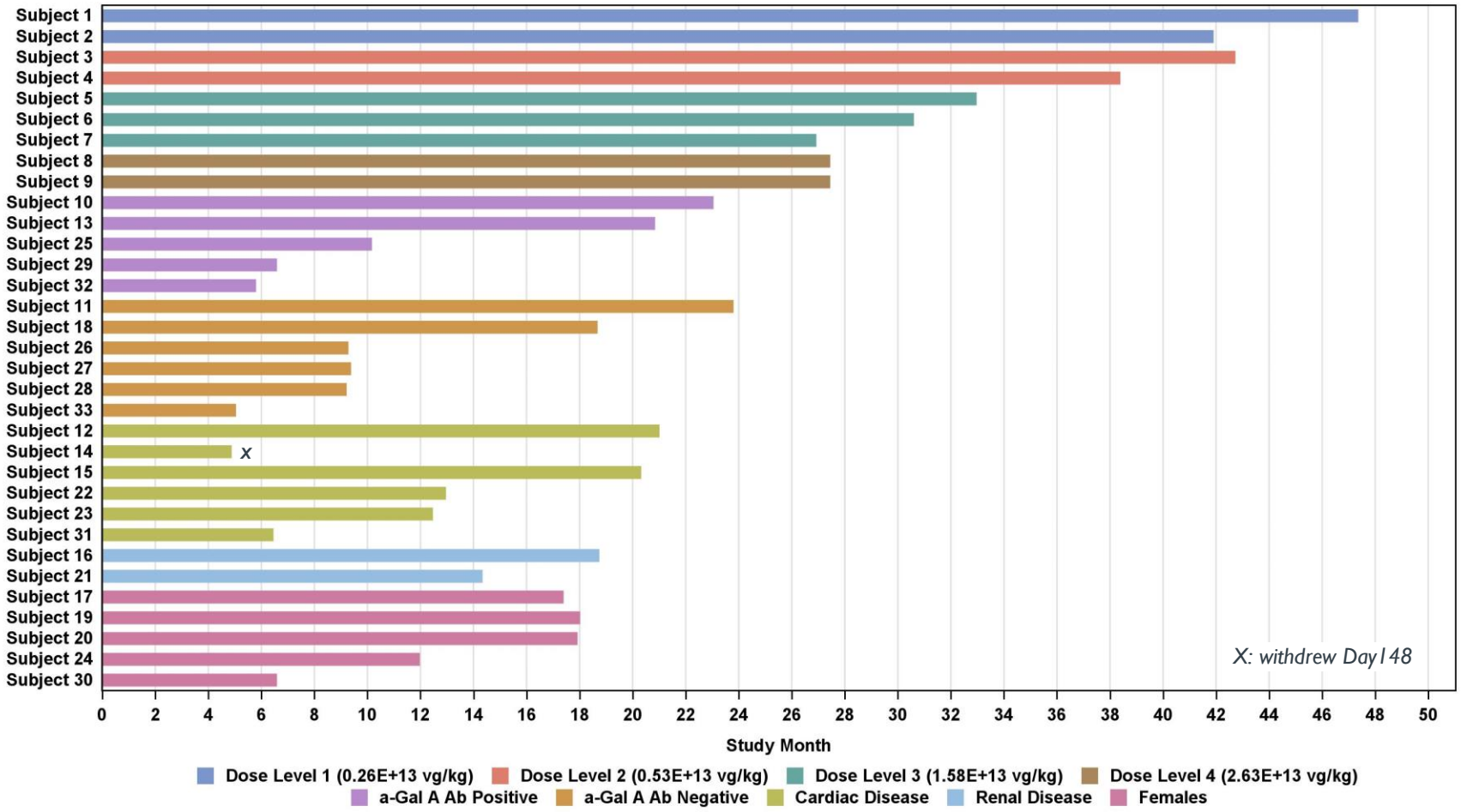
AE by preferred term	Treated subjects (n=33)	
	All grades	Grade 3-4
Pyrexia	20 (60.6%)	1 (3.0%) (G3)
COVID-19	12 (36.4%)	0
Nasopharyngitis	11 (33.3%)	0
Headache	12 (36.4%)	0
Fatigue	9 (27.3%)	0
Nausea	9 (27.3%)	0
Cough	5 (15.2%)	0
Diarrhea	5 (15.2%)	0
Myalgia	5 (15.2%)	1 (3.0%) (G3)
Hypotension	4 (12.1%)	0
Urinary tract infection	4 (12.1%)	0
Paresthesia	4 (12.1%)	0
Chills	4 (12.1%)	0

Data cut-off date: 12 September 2024
AE, adverse event; LFT, liver function test; TESAE, treatment-emergent serious adverse event;

- ST-920 was generally well-tolerated with majority of AEs being grade 1-2 in nature, as of the 12 September 2024 cut-off date.
- No LFT elevations requiring steroids
- TESAEs were reported in 4 subjects, all Grade 2 or Grade 3:
  - Left arm pain, non-cardiac chest pain, sepsis, stroke, shoulder enthesopathy
- No AEs led to study discontinuation
- No deaths

Follow-up for up to 47.3 months

- Median duration of follow-up: 18 months (20 weeks – 47.3 months)
- 23 subjects have ≥ 12 months of follow-up

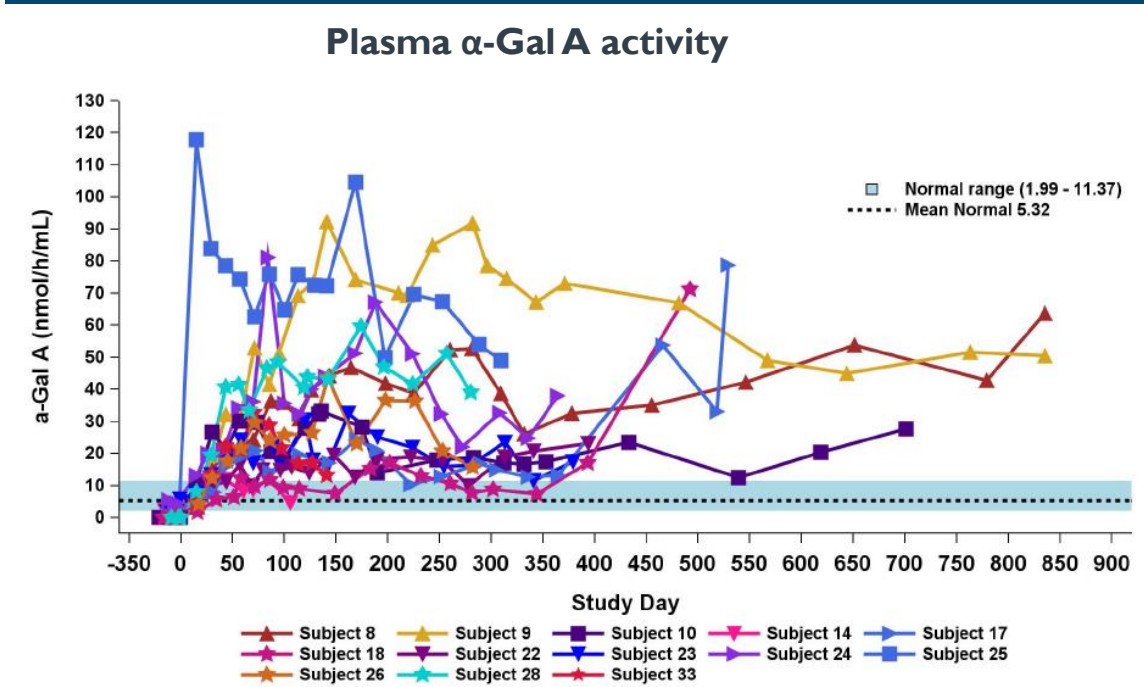


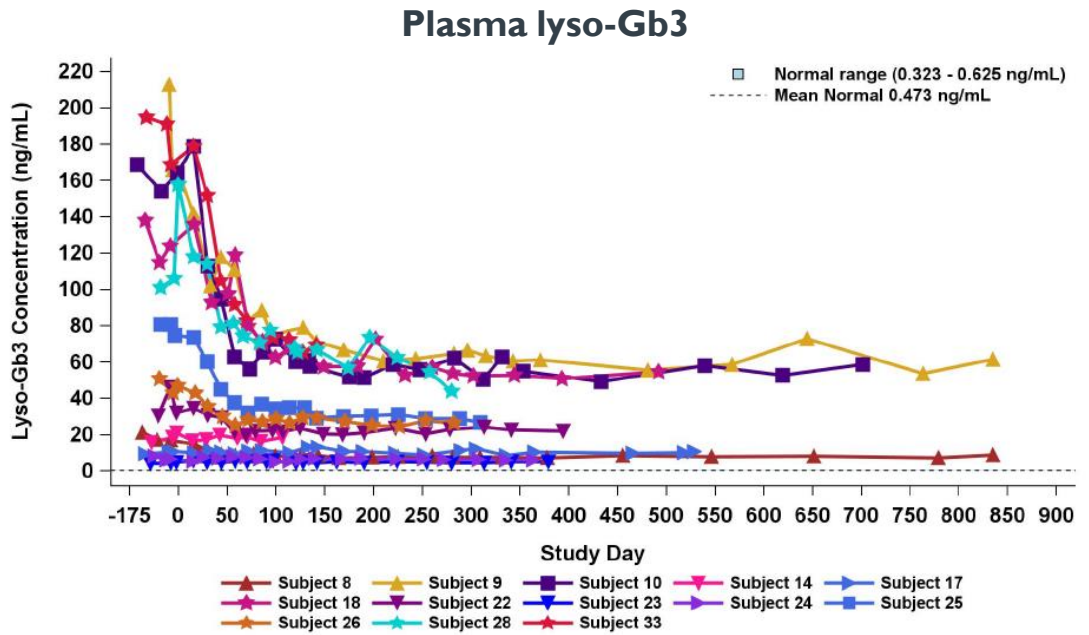
Data cut-off date: 12 September 2024

ST-920-driven plasma α-Gal A activity and reduction in lyso-Gb3 in ERT naïve/pseudo-naive subjects

- Sustained supraphysiological α-Gal A activity up to **27 months** for those naïve/pseudo-naïve subjects receiving the top dose ($2.63x10^{13}$ vg/kg) and **42 months** for all naïve/pseudo-naïve subjects, independent of dose
- Largest reductions in plasma lyso-Gb3 in subjects with highest levels at baseline
- Long-term stabilization of lyso-Gb3 levels

Plasma α-Gal A and lyso-Gb3 in ERT naïve/pseudo-naïve subjects receiving 2.63×10^{13} vg/kg (n=13)





Data cut-off date: 12 September 2024

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.

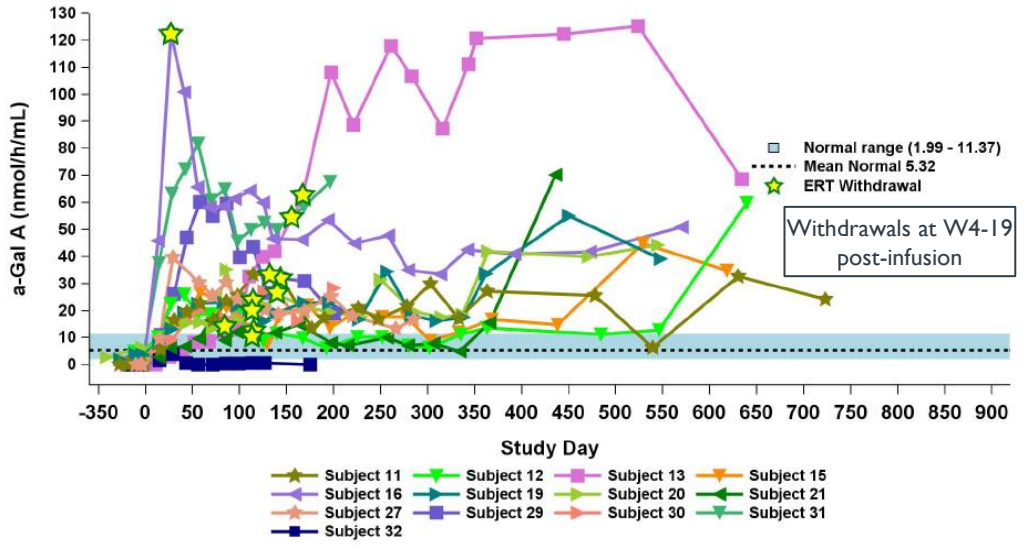
α-Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; vg/kg, vector genomes per kilogram of total body weight (as assessed by ddPCR)

All subjects have been withdrawn from ERT post-ST-920 infusion and all remain off ERT

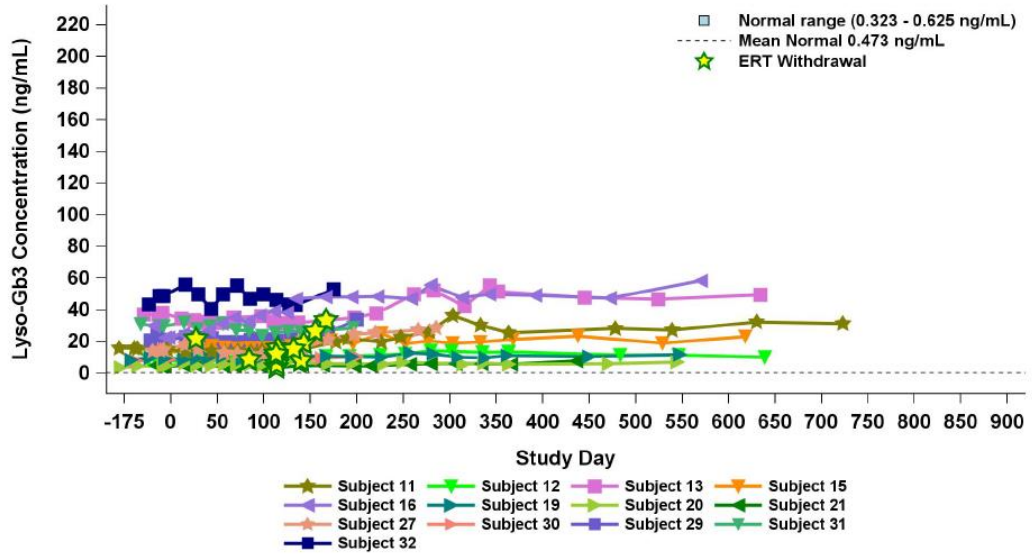
- Timing of ERT withdrawal was at discretion of the investigator, to occur no earlier than 8 weeks post-ST-920 dosing.
- 17 out of 18 ERT subjects withdrawn from ERT as of the data cut-off; the remaining one subject was withdrawn after the Sep'24 data cut. All 18 out of 18 ERT subjects remain off ERT.
- Plasma lyso-Gb3 levels remained stable following ERT withdrawal for up to **19 months** for ERT subjects receiving the top dose (2.63×10^{13} vg/kg) and **33 months** for all ERT subjects, independent of dose.

Plasma α-Gal A and lyso-Gb3 in ERT-treated subjects receiving 2.63×10^{13} vg/kg (n=13)

Plasma α-Gal A activity



Plasma lyso-Gb3



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α-Gal A activity measured using 3-hour reaction time. Normal range determined in healthy males and females.

α-Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; vg/kg, vector genomes per kilogram of total body weight (as assessed by ddPCR); W, week

For the 23 subjects with at least 1-year follow-up, a positive mean eGFR slope was observed

eGFR Slope at 1 year N=23	
Mean (SD), (95% CI)	3.061 (5.1), (0.863, 5.258)

eGFR slope for each subject is estimated using linear regression and then summarized

Data cut-off date: 12 September 2024
eGFR, estimated glomerular filtration rate; N, number; SD, standard deviation; CI, confidence interval.

Significant improvements in disease severity, quality of life and GI symptoms
(23 pts with ≥12 months follow-up)

FOS-MSSI:

- At 12m, 15/22 (68 %) of subjects improved their total MSSI score
- 7 subjects (including 4 on ERT) improved their FOS-MSSI category

SF-36 (12 mo):

- General Health score: +10.6 (n=21; p-value=0,0020)
  - +3-5 change is considered a minimal clinically important difference
- Significant improvements in physical component, bodily pain, physical, vitality, social function, and emotional scores

GSRS (GI Symptom Rating Scale) (12 mo)**:**

- Statistically significant improvement in GSRS score, Abdominal Pain, Indigestion, Diarrhoea and Constipation Scores, n=22

Subject	ERT status at Baseline	FOS-MSSI category Baseline	FOS-MSSI category Week 52	FOS-MSSI category Week 104	FOS-MSSI category Year 3	FOS-MSSI category Year 4
1	ERT	Moderate	Moderate		Moderate	**Mild**
2	Pseudo-naive	Mild	Mild	Mild	Mild	
3	Pseudo-naive	Moderate	Moderate	**Mild**	**Mild**	
4	ERT	Mild	Mild	Mild	Mild	
5	ERT	Moderate	**Mild**	Moderate		
6	ERT	Moderate	**Mild**	**Mild**	**Mild**	
7	ERT	Severe	**Moderate**	**Moderate**		
8	Naive	Moderate	**Mild**	**Mild**		
9	Naive	Moderate		Moderate		
10	Pseudo-naive	Moderate	Moderate	Moderate		
11	ERT	Moderate	Moderate	Moderate		
12	ERT	Mild	Mild	Mild		
13	ERT	Mild	Mild			
15	ERT	Mild	Mild			
16	ERT	Moderate	Moderate			
17	Naive	Moderate	**Mild**			
18	Naive	Moderate	Moderate			
19	ERT	Mild	Moderate			
20	ERT	Moderate	Moderate			
21	ERT	Moderate	**Mild**			
22	Naïve	Mild	Mild			
23	Naive	Mild	Mild			
24	Pseudo-naive	Moderate	Moderate			

Data cut-off date: 12 September 2024

Analysis of ST-920 treated subjects with ≥12 m follow-up (n=22). "Month 12" is Week 52 study timepoint. All p-values are unadjusted nominal p-values. ERT, enzyme replacement therapy; GI, gastrointestinal, FOS-MSSI, Fabry Outcome Survey adaptation of the Mainz Severity Score Index; SF-36, Short Form-36 (a 3-to-5-point change on any SF-36 score is the minimally clinically important difference)

Reduction or elimination of antibodies against α-Gal A

	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	Undetectable (W4)
Subject 13	5120	320	160	10
Subject 16	2560	640	40	Undetectable (W52)
Subject 25	160	Undetectable (W4)	160	Undetectable (W4)
Subject 31	80	Undetectable (W12)	10	Undetectable (W4)
Subject 32	20480	20480	640	320

Data cut-off date: 12 September 2024
α-Gal A, alpha-galactosidase A; Ab, antibody; NAb , neutralizing antibody; W, week; (-) denotes NAb testing not done when total Ab titer is 0

- Immunogenicity remains an issue with ERT leading to continuing organ impairment
- 10 subjects had measurable titers of total antibodies (Ab) or neutralizing antibodies (NAb) against α-Gal A associated with ERT at baseline
- After ST-920 treatment, total Ab or NAb titers decreased markedly in 9 subjects and became undetectable in 7 (70%)
- ST-920 treatment did not induce anti-α-Gal A antibodies in seronegative subjects

Summary

- 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 and no discontinuation based on ST-920
  - No prophylactic steroids or other immunomodulatory agents administered. No LFT elevations requiring steroids.

- **Durable efficacy** was demonstrated with supraphysiological α-Gal A activity up to **27 months** for those receiving the top dose ($2.63x10^{13}$ vg/kg) and **47 months** for all subjects independent of dose

- **Positive mean eGFR slope** observed in the 23 patients that have reached 1-year follow-up, indicating improvements in renal function

- **Clinically and statistically significant QOL improvements**
  - 68 % improvement in FOS-MSSI
  - Improvement in SF-36 scores
  - Improvements in gastrointestinal symptoms

- All 18 subjects who discontinued ERT remain off ERT, for up to 33 months

- Total or neutralizing α-Gal A antibodies decreased markedly in 9 subjects and became undetectable in 7 (70%)

- ***ST-920 has potential as a one-time, durable treatment option for Fabry disease that can improve patient outcomes***

Data cut-off date: 12 September 2024

Acknowledgments

Investigators:

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