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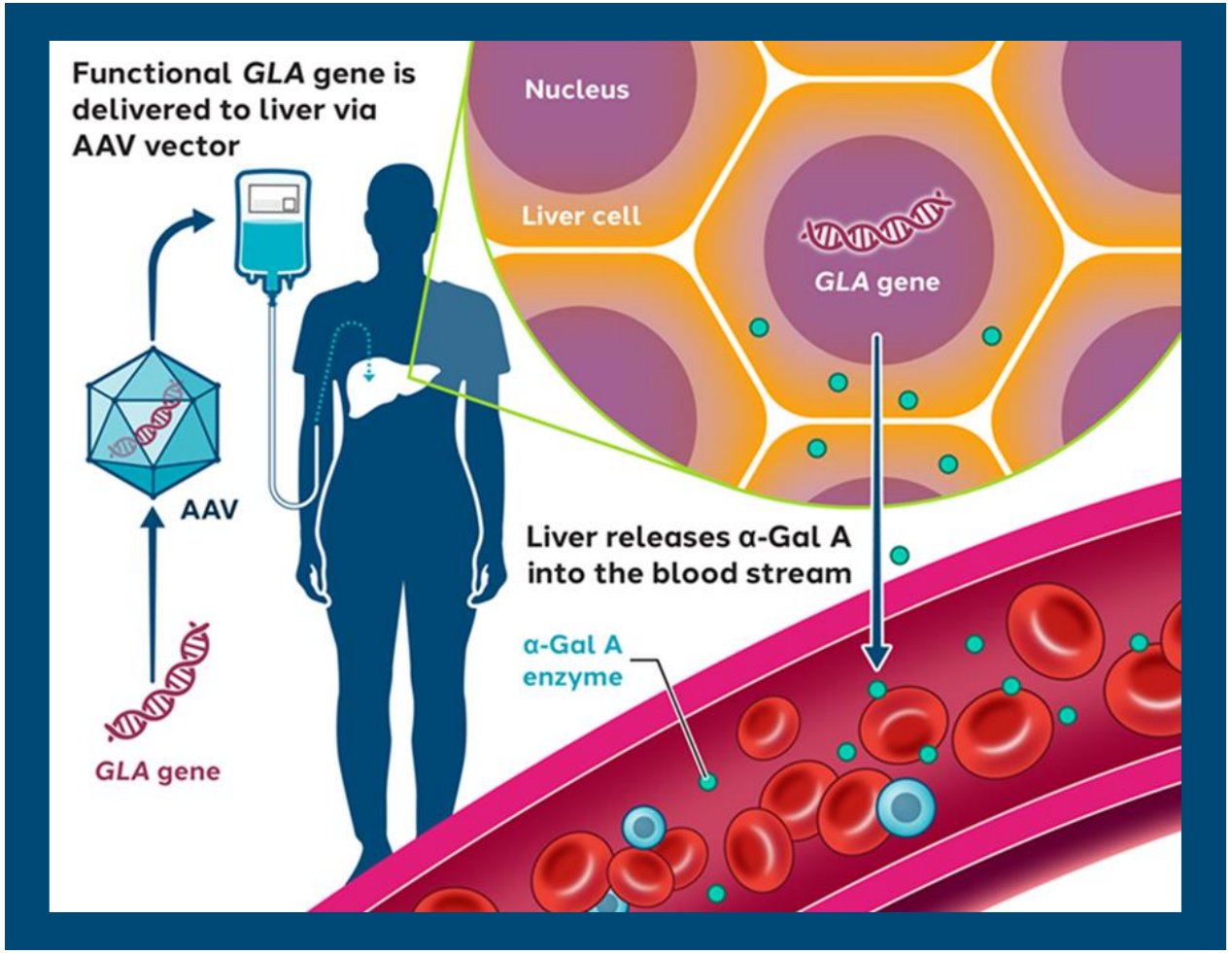
ST-920 employs a recombinant AAV2/6 vector with human GLA cDNA for continuous, liver-specific α-Gal-A expression



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

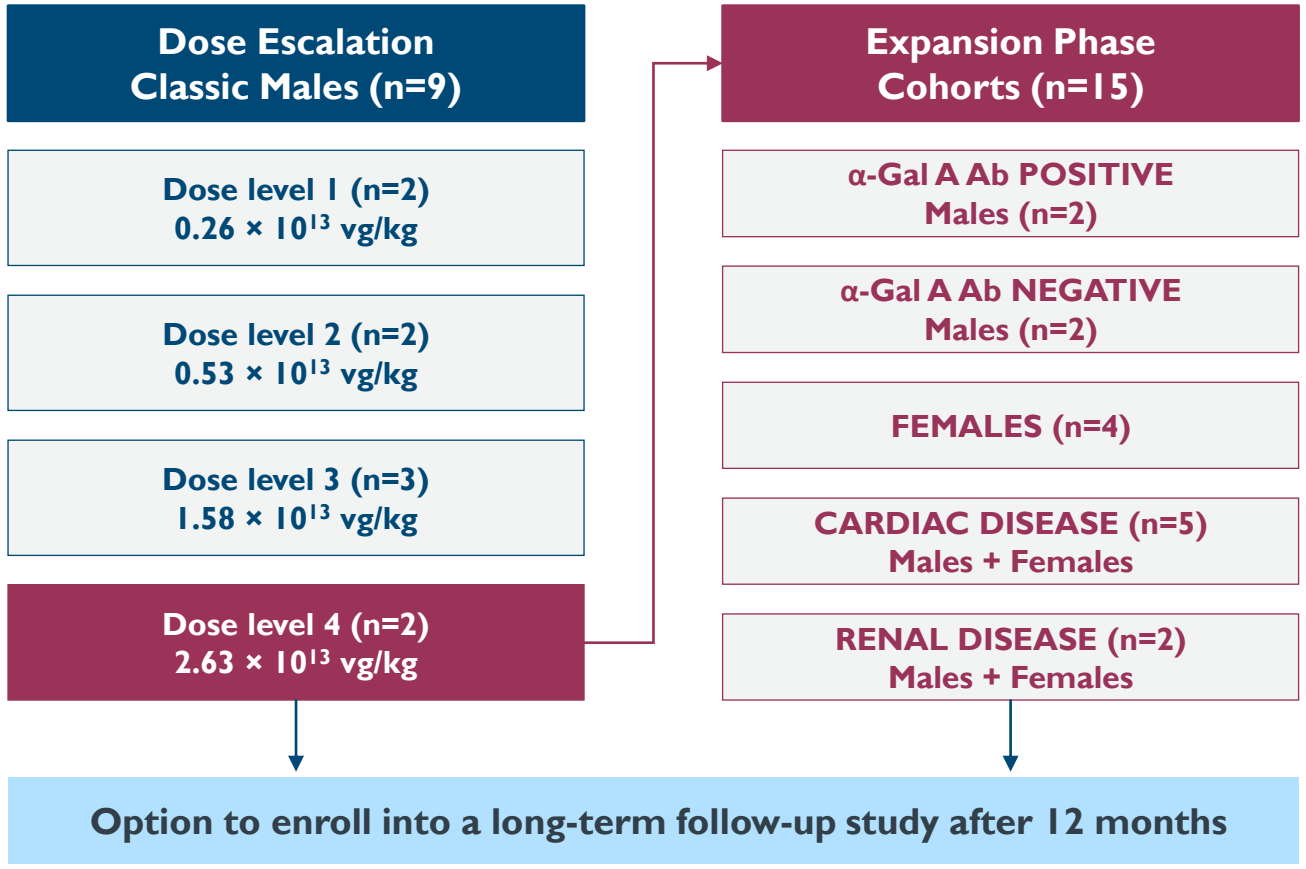
- Age ≥18 with symptomatic Fabry disease
  - ERT-naïve or pseudo-naïve (no ERT in prior 6 months)
  - On ERT
- eGFR ≥40 mL/min/1.73m^2
- No neutralizing antibodies to AAV6

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 (+ renal Gb3 inclusions)
- 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=15)	All (n=24)
Age, median (range)	42 (22-50)	45 (21-67)	44 (21-67)
Sex (M:F)	9:0	6:9	15:9
ERT status (n,%):			
• Naïve	2 (22%)	4 (27%)	6 (25%)
• Pseudo-naïve	2 (22%)	3 (20%)	5 (21%)
• On ERT	5 (56%)	8 (53%)	13 (54%)
Baseline Fabry symptoms (n,%):			
• Cornea verticillata	4 (44%)	8 (53%)	12 (50%)
• Acroparesthesia	3 (33%)	3 (20%)	6 (25%)
• Anhidrosis	1 (11%)	2 (13%)	3 (13%)
• Angiokeratoma	2 (22%)	7 (47%)	9 (38%)
$eGFR_{CKD-EPI}$ category, n (%):			
• >90 ml/min/1.73 m^2	5 (56%)	9 (60%)	14 (58%)
• 60-90 ml/min/1.73 m^2	3 (33%)	3 (20%)	6 (25%)
• 40-<60 ml/min/1.73 m^2	1 (11%)	3 (20%)	4 (17%)

Data cut-off date: 19 September 2023
eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); ERT, enzyme replacement therapy

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

Summary of treatment-emergent AEs in >2 subjects

AE by preferred term	Treated subjects (n=24)	
	All grades	Grade 3-4
Pyrexia	15 (63%)	1 (4%) (G3)
Headache	9 (38%)	0
COVID-19	9 (38%)	0
Fatigue	7 (29%)	0
Nasopharyngitis	6 (25%)	0
Diarrhea	4 (17%)	0
Hypotension	4 (17%)	0
Nausea	4 (17%)	0
Arthralgia	3 (13%)	0
Viral infection	3 (13%)	0
Myalgia	3 (13%)	1 (4%) (G3)
Neck pain	3 (13%)	0

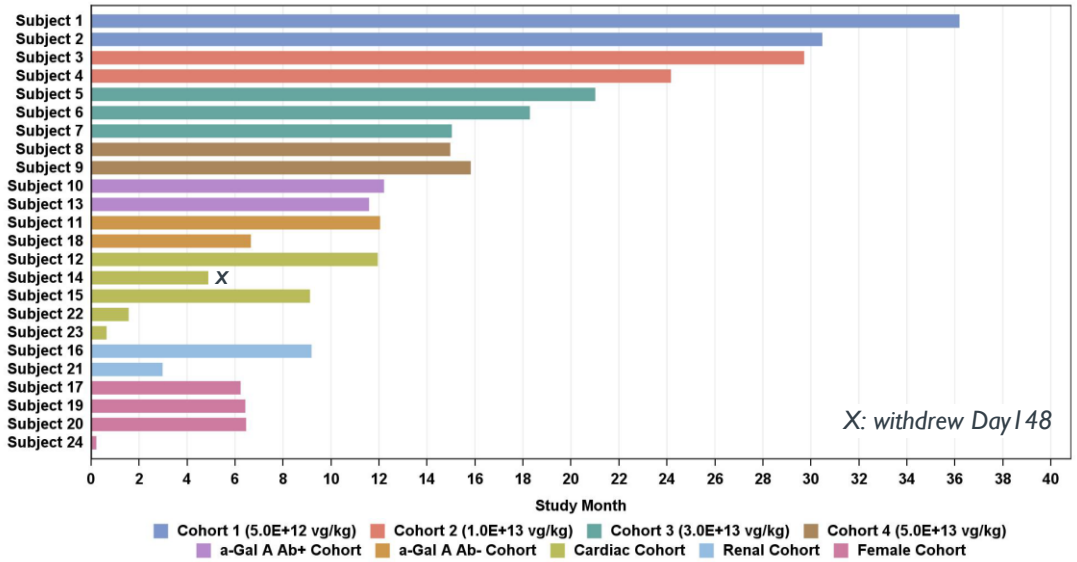
Data cut-off date: 19 September 2023
AE, adverse event; ALT, alanine aminotransferase; LFT, liver function test; n, number of subjects with AE; TESAE, treatment-ermergent serious adverse event; ULN, upper limit of normal; vg/kg, vector genomes per kilogram of total body weight (as assessed by ddPCR)

- ST-920 was generally well-tolerated with majority of AEs being grade 1-2 in nature, as of the 19 Sep 2023 cut-off date
- 3 subjects (12%) experienced post-infusion hypotension:
  - Grade 2, steroids administered (n=2)
  - Grade 1, saline bolus administered (n=1)
- No LFT elevations requiring steroids
  - Steroids administered for ALT ↑ ≥2x baseline and >ULN, or ↑ >2x baseline x 2 consecutive values
  - Prophylactic steroids/other immunosuppressive agents were not required prior to dosing
- TESAEs were reported in 4 subjects: left arm pain (0.53×10^{13} vg/kg); sepsis (1.58×10^{13} vg/kg); enthesopathy, stroke/ischemic stroke (2.63×10^{13} vg/kg)
- No AEs led to study discontinuation

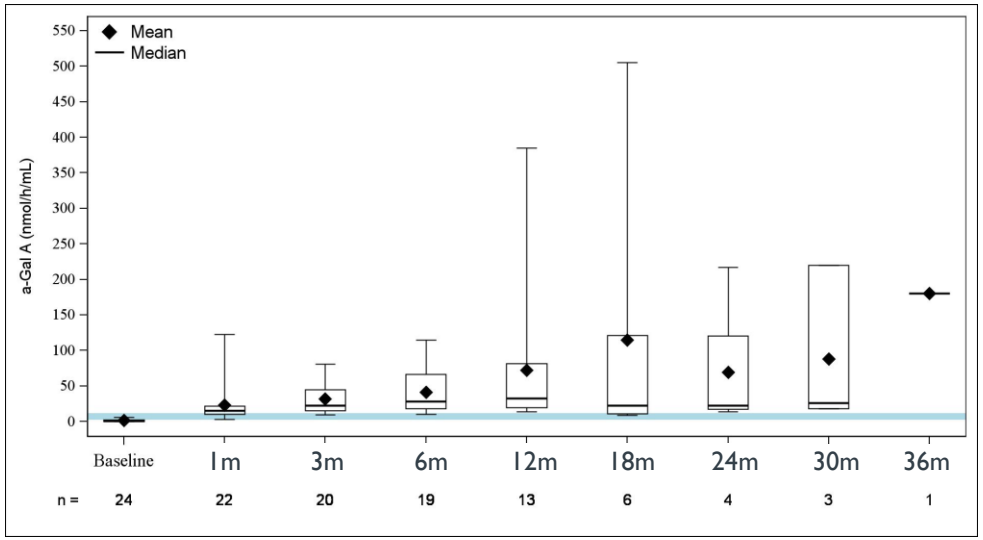
Follow-up for up to 36 months

- Median duration of follow-up: 51.1 weeks (0.9 wk - 36.2 months)
- 13 subjects have ≥ 12 months of follow-up

- Supraphysiological levels of α-Gal A activity were maintained for up to 36.2 months



α-Gal A normal range

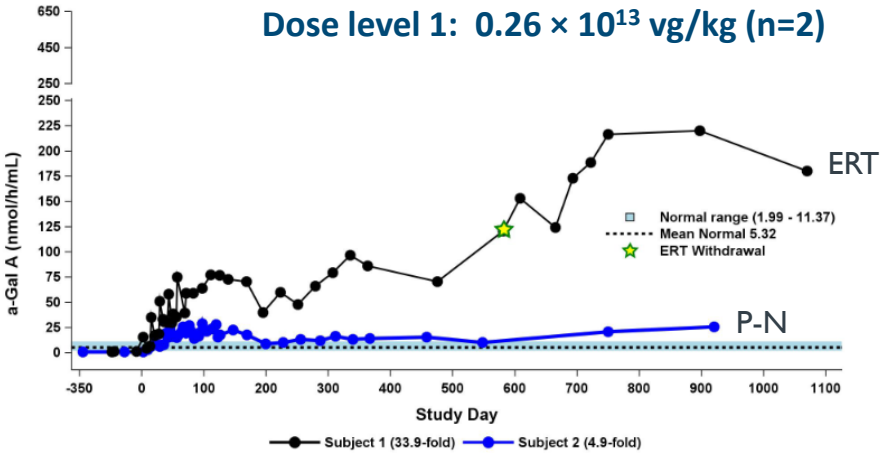


Data cut-off date: 19 September 2023

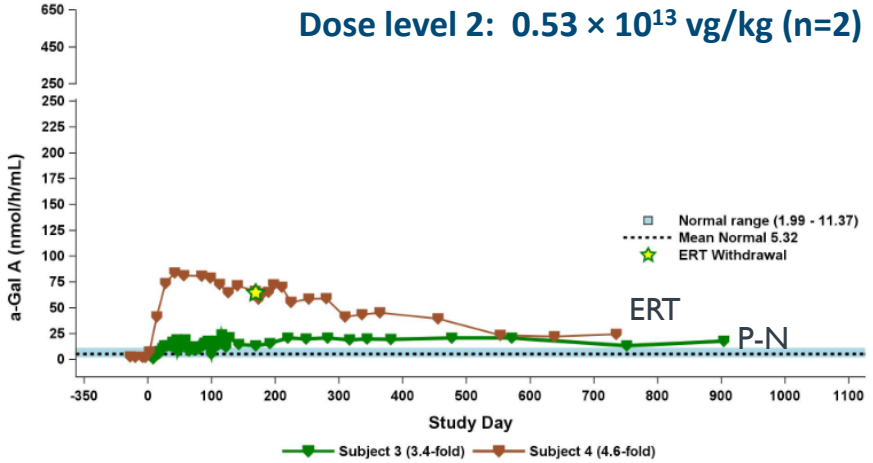
Dose-dependent effect on α-Gal A activity in naïve/pseudo-naïve subjects

2.63×10[13] vg/kg selected for expansion phase

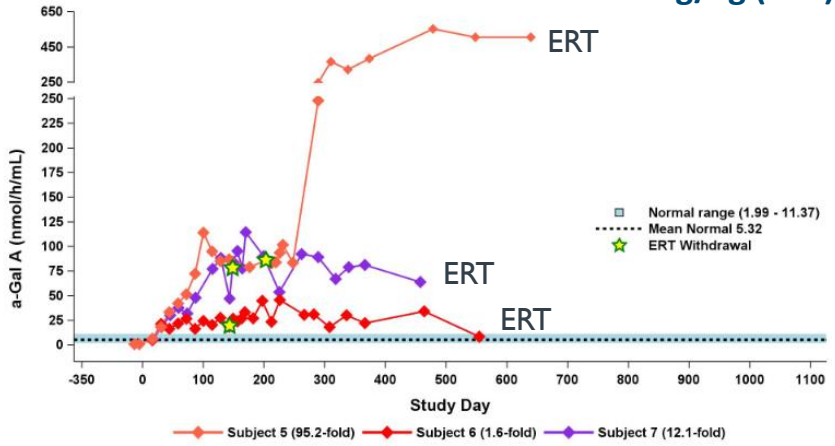
Dose level 1: 0.26 × 10[13] vg/kg (n=2)



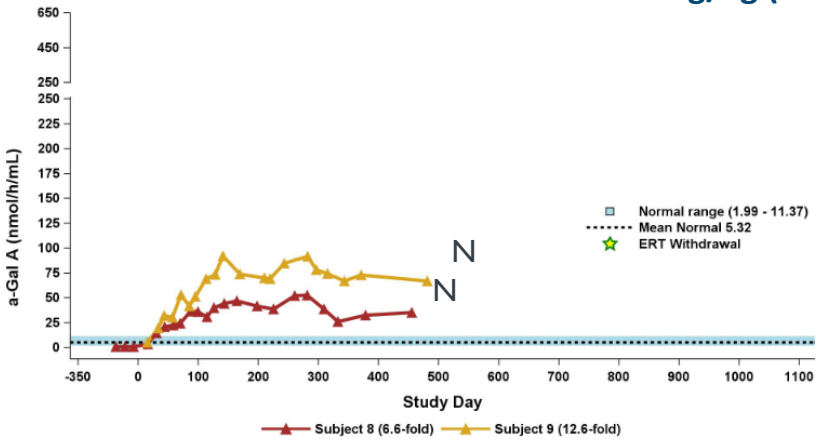
Dose level 2: 0.53 × 10[13] vg/kg (n=2)



Dose level 3: 1.58 × 10[13] vg/kg (n=3)



Dose level 4: 2.63 × 10[13] vg/kg (n=2)



Data cut-off date: 19 September 2023

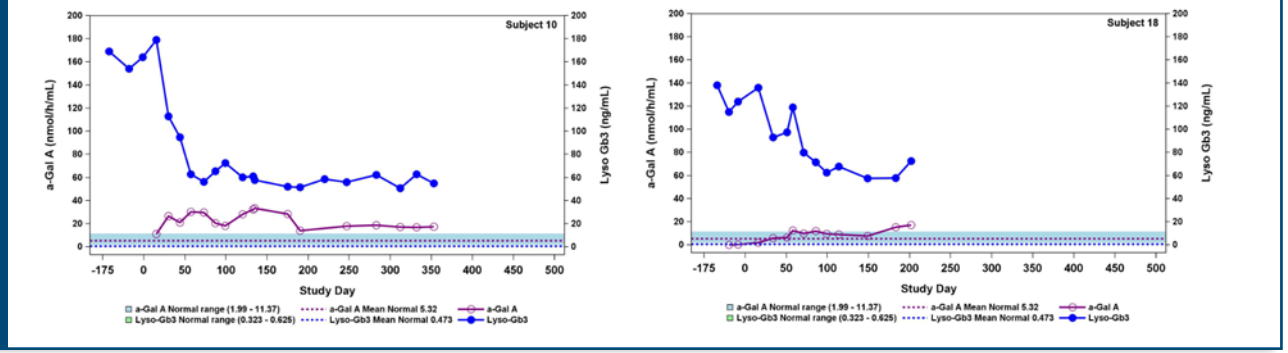
α-Gal A activity measured using 3-hour reaction time. Normal range determined in healthy males and females. Data points > Study Day 365 are from long-term follow-up study.

α-Gal A, alpha-galactosidase A; vg/kg, vector genomes per kilogram of total body weight (as assessed by ddPCR); ERT, ERT-treated at baseline; N, ERT-naïve; P-N, pseudo-naïve, no ERT in ≥6 months prior to screening

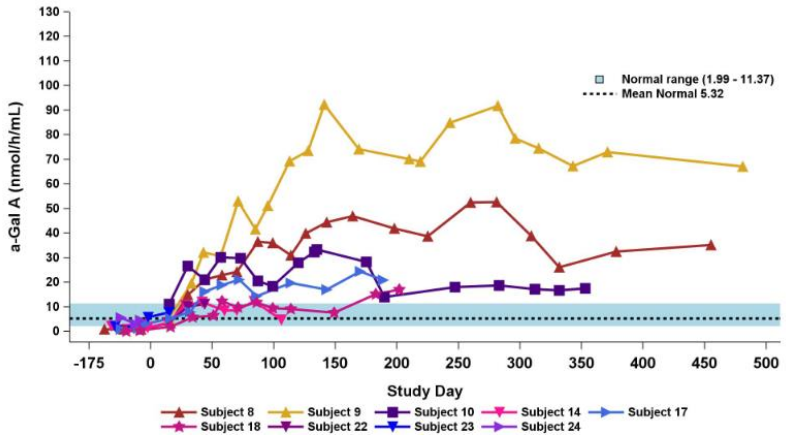
ST-920-driven plasma α-Gal A activity and reduction in lyso-Gb3 in ERT naïve/pseudo-naive subjects receiving 2.63×10^{13} vg/kg (n=9)

- Sustained supraphysiological α-Gal A activity up to nearly 500 days
- Largest reductions in plasma lyso-Gb3 in subjects with highest levels at baseline
- Long-term stabilization of lyso-Gb3 levels

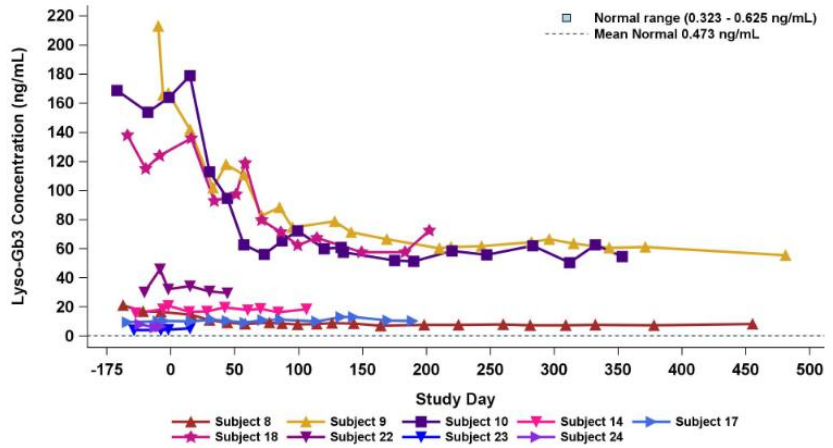
Large reduction in plasma lyso-Gb3 possible with modest levels of continuous α-Gal A activity



Plasma α-Gal A activity



Plasma lyso-Gb3



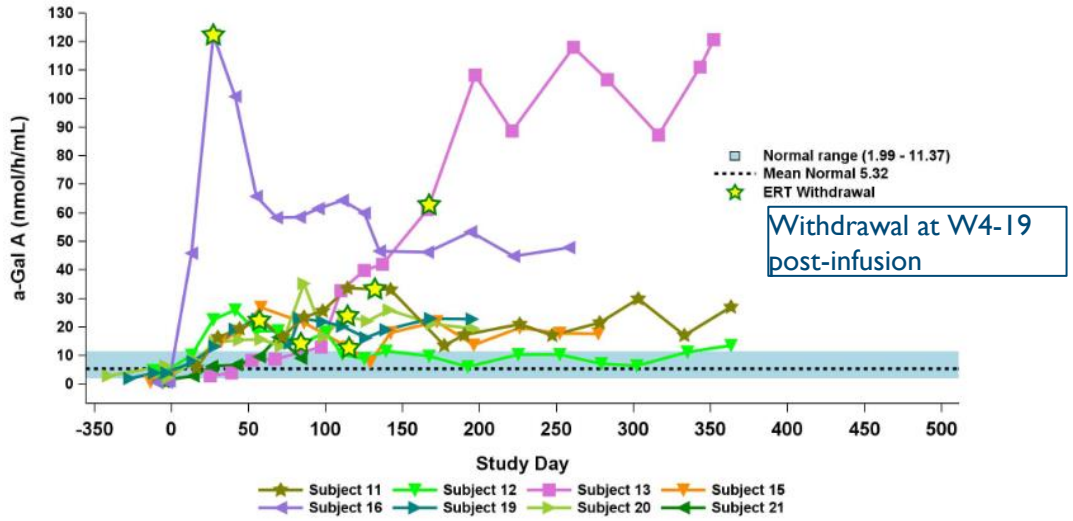
Data cut-off date: 19 September 2023
α-Gal A activity measured using 3-hour reaction time. Normal range determined in healthy males and females. Long Term Follow-up Data: Data points > Study Day 365.
α-Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; vg/kg, vector genomes per kilogram of total body weight (as assessed by ddPCR)

All subjects withdrawn from ERT post-ST-920 infusion remain off ERT

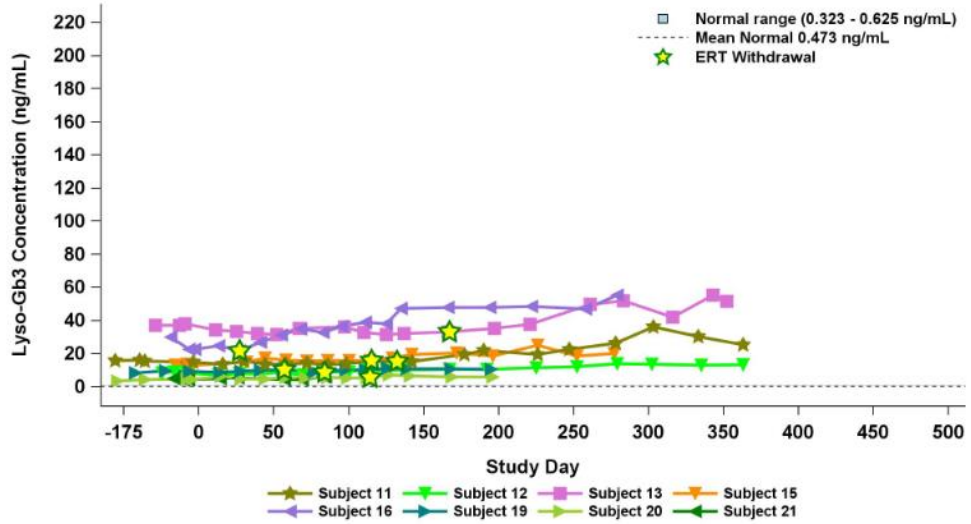
- Timing of ERT withdrawal was at the discretion of the investigator, to occur no earlier than 8 weeks post-ST-920 dosing
- All 12 subjects withdrawn from ERT remain off ERT; 11 maintain sustained supraphysiological levels of α-Gal A activity for up to ~19 months (1 sustained physiological levels) as of the data cut-off
- Plasma lyso-Gb3 levels remained stable following ERT withdrawal for up to 1 year (last study timepoint)

Plasma α-Gal A and lyso-Gb3 in ERT-treated subjects receiving 2.63×10^{13} vg/kg (n=8)

Plasma α-Gal A activity



Plasma lyso-Gb3



Data cut-off date: 19 September 2023
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

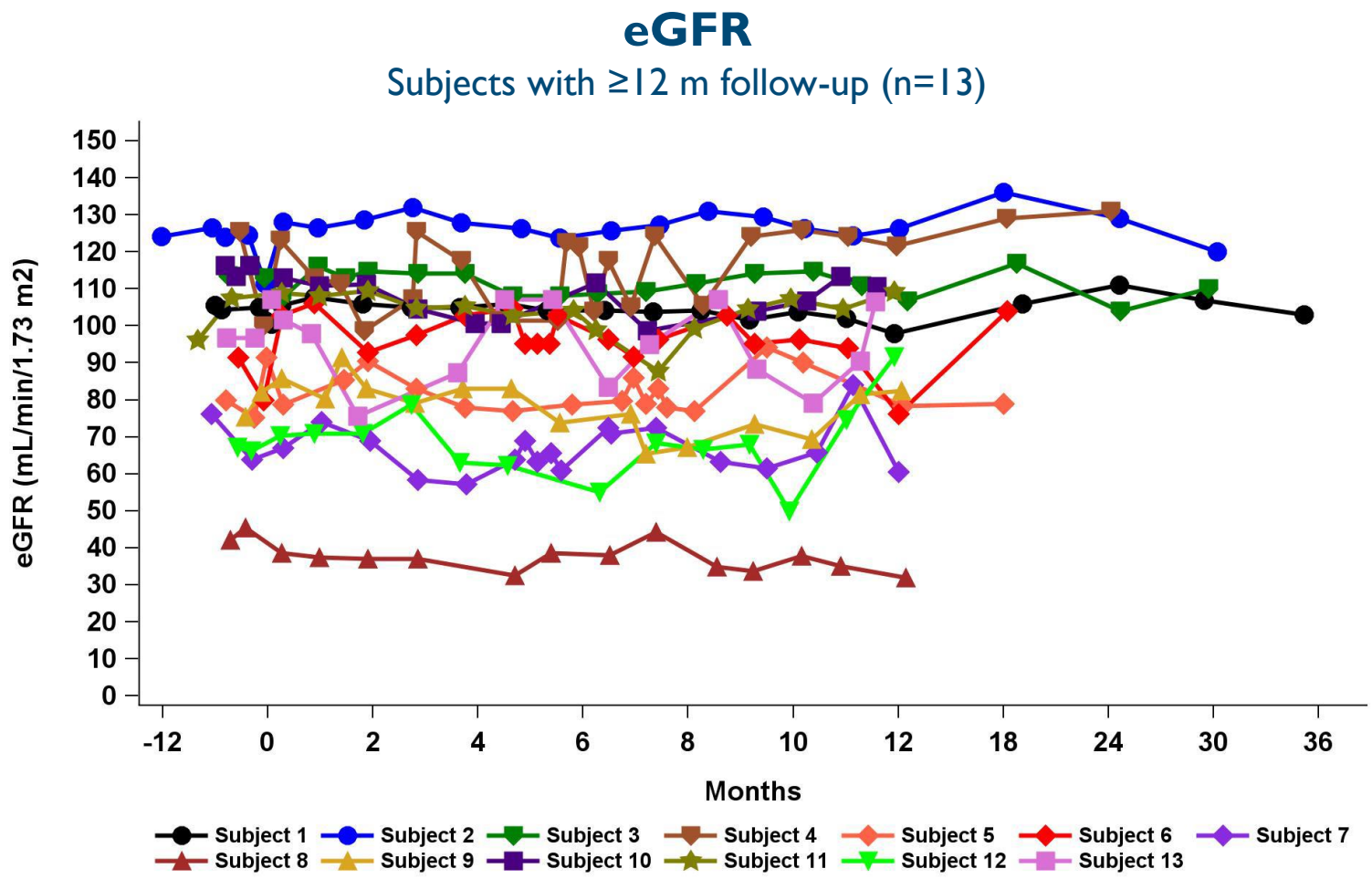
Maintained stability of renal function in subjects with ≥12 m of follow-up

Mean annualized eGFR slope:

-0.915 mL/min/1.73m^2 /year
(95% CI: -4.1, 2.3)

Median eGFR at baseline:

96.7 mL/min/ 1.73m^2



Data cut-off date: 19 September 2023
eGFR, estimated glomerular filtration rate (mL/min/1.73m2) by 2009 CKD-EPI creatinine equation; 95% CI, 95% confidence interval bounds

Significant improvements in disease severity, quality of life and GI symptoms

FOS-MSSI:

- Mean change from baseline at Month 12 in age-adjusted score: **-3.96** (95% CI: [-7.4.-0.5]), p=0.0269
- 9/13 (69%) improved their total MSSI score from baseline at Month 12
- 4 subjects (1 treatment-naïve) improved their disease category
- Improvements in each of the 4 MSSI sections were observed
- Subjects on ERT at baseline then withdrawn from ERT:
  - 6/8 (75%) improved scores (by -3.5 to -14 points)
  - 3/8 (38%) improved their disease category

SF-36: Mean change from baseline at Month 12 in

- General Health score: **+10.5** (95% CI: [2.3, 18.6], p=0.0158)
- Physical Component score: **+4.395** (95% CI: [1.1, 7.7], p=0.0140)

GSRS (GI Symptom Rating Scale):

- Mean change from baseline at Month 12 = **-0.26**, 95% CI: [-0.5, -0.0], p=0.0226

Subject	ERT at Baseline?	FOS-MSSI category: Baseline	FOS-MSSI category: Week 52
1	ERT	Moderate	Moderate
2	Pseudo-naive	Mild	Mild
3	Pseudo-naive	Moderate	Moderate
4	ERT	Mild	Mild
5	ERT	Moderate	**Mild**
6	ERT	Moderate	**Mild**
7	ERT	Severe	**Moderate**
8	Naive	Moderate	**Mild**
9	Naive	Moderate	Moderate
10	Pseudo-naive	Moderate	Moderate
11	ERT	Moderate	Moderate
12	ERT	Mild	Mild
13	ERT	Mild	Mild

Analysis of ST-920 treated subjects with ≥12 m follow-up (n=13). "Month 12" is Week 52 study timepoint. All p-values are unadjusted nominal p-values. Data cut-off date: 19 September 2023
ERT, enzyme replacement therapy; 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	-
Subject 13	5120	320	160	10
Subject 16	2560	Undetectable (W36)	40	-

Data cut-off date: 19 September 2023
α-Gal A, alpha-galactosidase A; Ab, antibody; NAb , neutralizing antibody; W, week; (-) denotes NAb testing not done when total Ab titer is 0

- Progressive organ impairment linked to immunogenicity remains an issue with ERT
- 7 subjects had measurable titers of total antibodies (Ab) or neutralizing antibodies (NAb) against α-Gal A associated with ERT
- After ST-920 treatment, total Ab or NAb titers decreased markedly in all 7 subjects and became undetectable in 5 (71%)
- 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:
  - No prophylactic steroids/other immunomodulatory agents administered
  - No LFT elevations requiring steroids
- Durable efficacy was demonstrated, with supraphysiological levels of α-Gal A activity maintained for up to 36.2 months
  - Largest plasma lyso-Gb3 reductions seen in naïve/pseudo-naive subjects with highest baseline values
- Compared to baseline, the 13 subjects with ≥12 months of follow-up showed:
  - Renal function remained stable
  - Significant improvement in FOS-MSSI disease severity score, with 38% of subjects on ERT improving in disease severity category
  - Significant improvement in SF-36 QoL and GSRS GI symptom scores
- All 12 subjects who discontinued ERT remain off ERT for up to 19 months, as of the data cut-off
  - 11/12 maintain sustained supraphysiological α-Gal A activity (1 with sustained α-Gal A activity in normal physiologic range)
  - 75% (6/8) had an improved disease severity score at 12 months compared to their baseline severity score on ERT
- Total or neutralizing α-Gal A antibodies decreased markedly in 7 subjects and became undetectable in 5 (71%)
- ***ST-920 has potential as a one-time, durable treatment option for Fabry disease that can improve patient outcomes***

Acknowledgments

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