Preliminary Results of the STAAR Study, a Phase I/II Study of Isaralgagene Civaparvovec (ST-920) Gene Therapy in Adults With Fabry Disease

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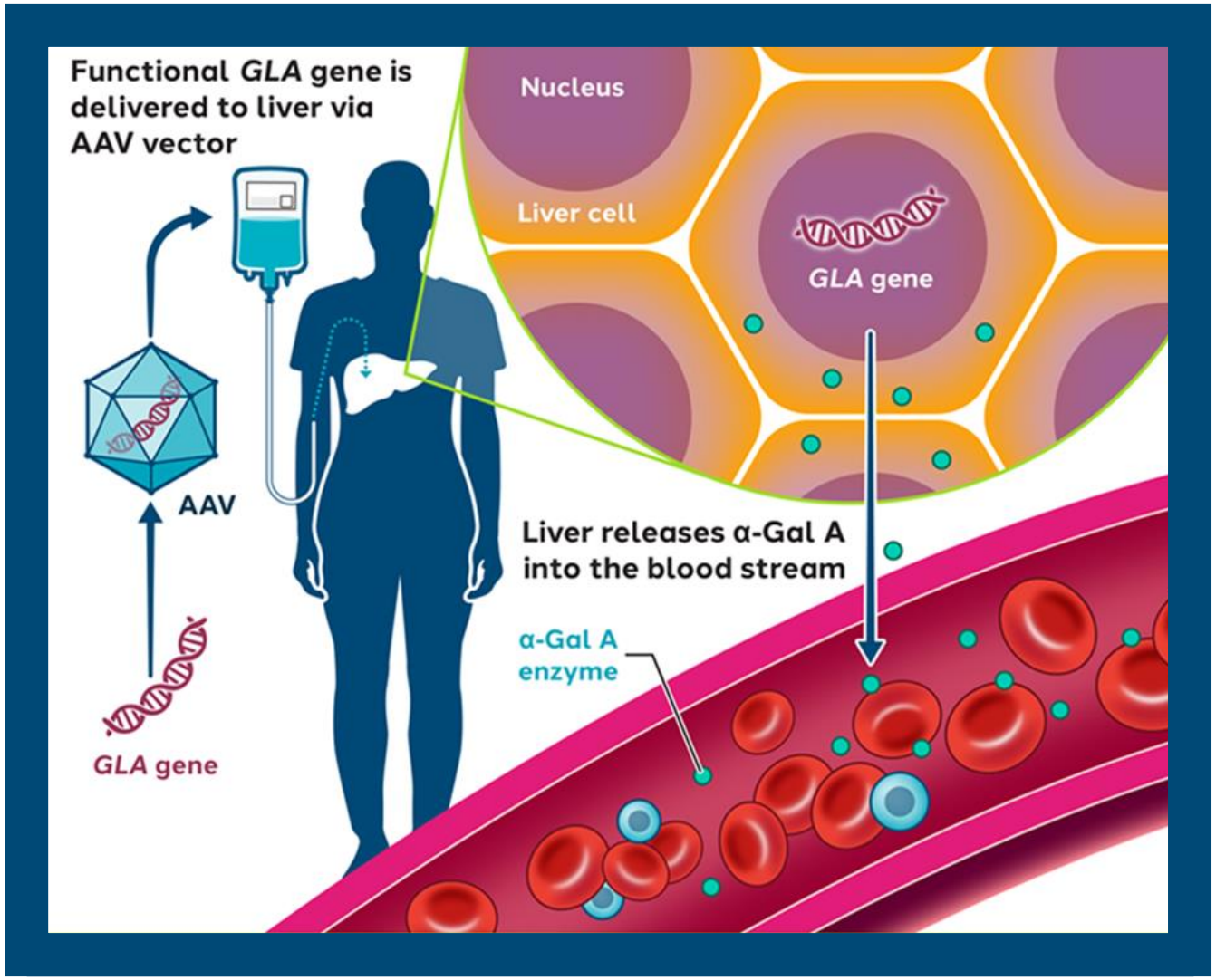
Isaralgagene Civaparvovec (ST-920): One-time, Liver-directed Gene Therapy Candidate for the Treatment of Fabry Disease



Goals of Treatment

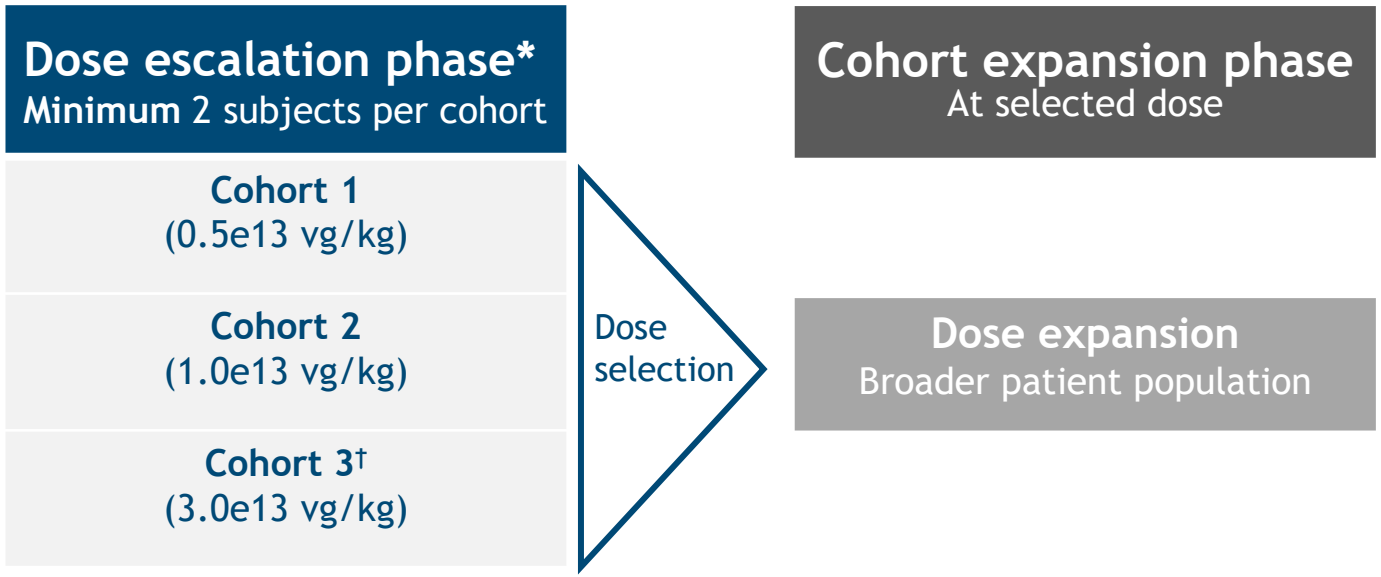
- Administer a one-time infusion, without the need for preconditioning
- Deliver long-lasting improvement of symptoms most important to patients
- Eliminate the need for biweekly ERT infusions

AAV, adeno-associated virus; ERT, enzyme replacement therapy; *GLA*, galactosidase alpha.

STAAR Study Design and Objectives

A Phase 1/2, global, open-label, single-dose, dose-ranging multicenter study to assess the safety and tolerability of ST-920, an AAV2/6 human α-Gal A gene therapy in patients with Fabry disease

STUDY DESIGN



*Safety and efficacy data of each cohort were reviewed by a safety monitoring committee prior to dose escalation.
†**Protocol supports addition of Cohort 4 at a higher dose level, if required.**

ENTRY CRITERIA

- Patients ≥18 years of age with Fabry disease
- On ERT regimen, or ERT-naïve, or ERT-pseudo-naïve (no ERT treatment in the prior 6 months)

PRIMARY OBJECTIVE

- Assess safety and tolerability of ST-920

SECONDARY OBJECTIVES

- Assess α-Gal A activity and the presence of its substrates in plasma over time
- Assess impact of ST-920 on ERT administration required for subjects on ERT
- Assess impact of ST-920 on renal and cardiac function
- Assess clinical impact of ST-920 on Fabry disease (including QoL)

ERT, enzyme replacement therapy; QoL, quality of life; vg/kg, vector genomes per kilogram of body weight.

Phase 1/2 STAAR Study: Baseline Subject Characteristics

	Cohort 1 (n=2) 0.5e13 vg/kg		Cohort 2 (n=2) 1.0e13 vg/kg		Cohort 3 (n=1) 3.0e13 vg/kg
	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Age (years)	48	25	42	22	39
On ERT	Yes	No; pseudo-naïve	No; pseudo-naïve	Yes	Yes
Plasma α-Gal A activity (nmol/h/mL)*	1.54	0.92	Below LOQ	2.44	0.85
Plasma lyso-Gb3 (ng/mL)*	22.1	18.1	83.2	11.1	32.7
Primary disease signs and symptoms	• Hypohidrosis • Tinnitus and vertigo • Left ventricular hypertrophy • Palpitations • Anemia • Leg edema	• Anhidrosis • Tinnitus • Acroparesthesia† • Sinus bradycardia • Left ventricular hypertrophy	• Hypohidrosis • Tinnitus and vertigo • Acroparesthesia† • ECG sinus arrhythmia	• Hypohidrosis • Neuropathic pain • Aortic root dilation	• Tinnitus • High frequency hearing loss • Acroparesthesia† • Sinus bradycardia • Loose stool and constipation
Renal function (eGFR)*,‡	101.4	111.4	112.9	100	91.5
Pre-existing α-Gal A Abs	Positive	Negative	Positive	Positive	Positive
Mutation	G621D	C422T	W340R	S297Y	Q283X

All subjects are male with classic Fabry disease.

*The time point immediately preceding ST-920 administration was presented as the baseline value.
†Burning, tingling, or numbness in the extremities.
‡eGFR (mL/min/1.73 m^2) was calculated using the CKD-EPI.
Ab, antibody; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LOQ, limit of quantitation; lyso-Gb3, globotriaosylsphingosine.

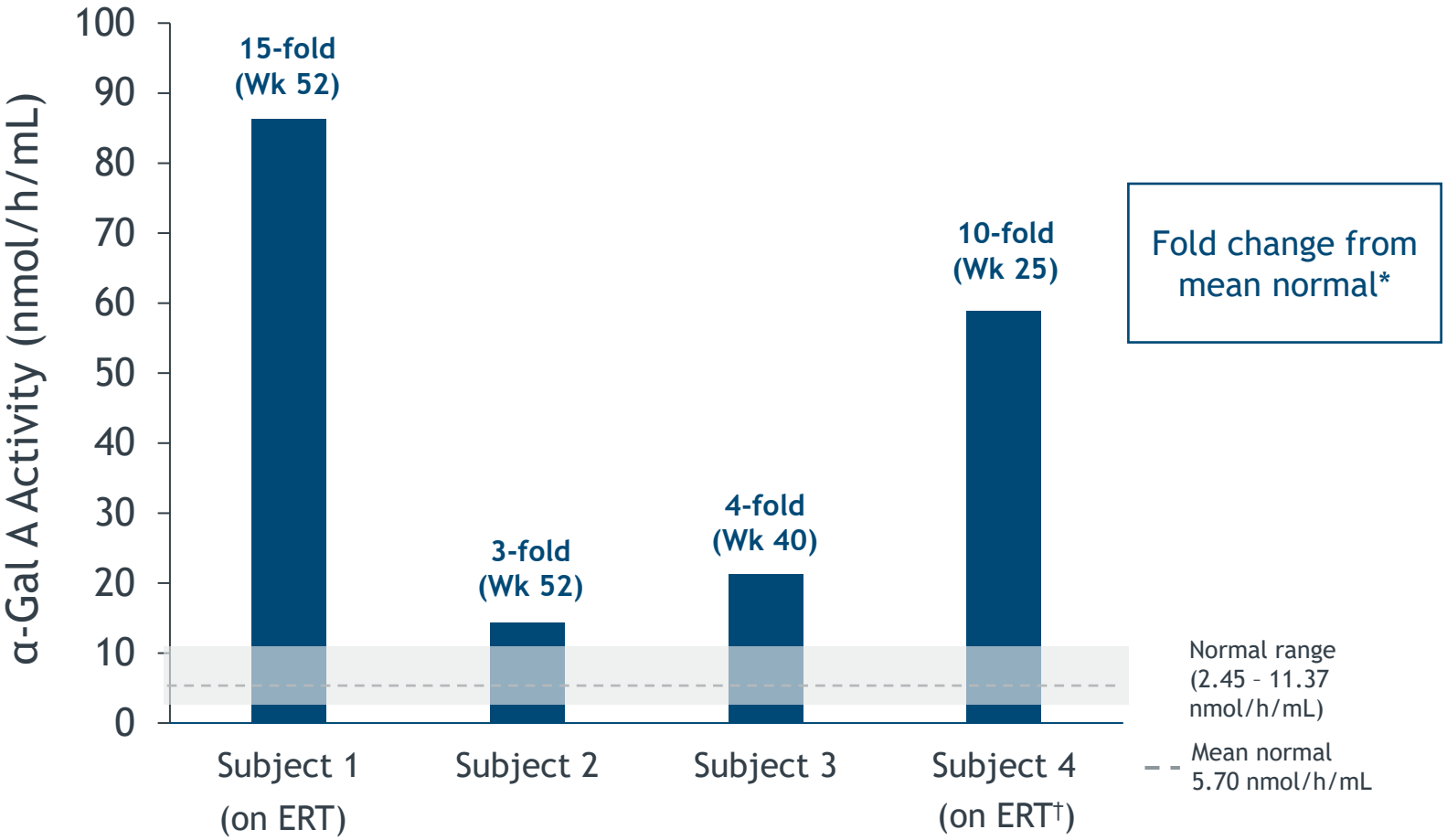
Phase 1/2 STAAR Study: Safety and Tolerability

MedDRA Preferred Term	Cohort 1 (0.5e13 vg/kg) (n=2)		Cohort 2 (1.0e13 vg/kg) (n=2)		Cohort 3 (3.0e13 vg/kg) (n=1)		Overall (N=5)	
	n	Events	n	Events	n	Events	n	Events
Treatment-related adverse events (total)	**1**	**3**	**1**	**2**	**1**	**6**	**3**	**11**
Hemoglobin decreased	1	1	0	0	0	0	1	1
Platelet count increased	1	1	0	0	0	0	1	1
Rash	1	1	0	0	0	0	1	1
Pyrexia	0	0	1	2	1	1	2	3
Headache	0	0	0	0	1	1	1	1
Myalgia	0	0	0	0	1	1	1	1
Fatigue	0	0	0	0	1	1	1	1
Abdominal pain	0	0	0	0	1	1	1	1
Frequent bowel movements	0	0	0	0	1	1	1	1

As of the cutoff date of November 9, 2021, safety data were evaluated from the 5 subjects in dose cohorts 1-3 (0.5e13 vg/kg, 1.0e13 vg/kg, and 3.0e13 vg/kg); length of follow-up ranged from 3-52 weeks (Subjects 1 and 2, 52 weeks; Subject 3, 40 weeks; Subject 4, 25 weeks; Subject 5, 3 weeks).
MedDRA, Medical Dictionary for Regulatory Activities; vg/kg, vector genomes per kilogram of body weight.

- Isaralgagene civaparvovec (ST-920) was generally well tolerated as of the cutoff date
- There were no liver enzyme elevations requiring steroid treatment
- No treatment-related serious adverse events were reported
- All treatment-related adverse events were Grade 1 (mild)

Phase 1/2 STAAR Study: Plasma α-Gal A Activity



- Elevated α-Gal A activity was maintained through the last sampling point for Subjects 1-4: up to 1 year for the first 2 subjects treated
- α-Gal A activity is within normal at week 2 for Subject 5
- Subject 4 was withdrawn from ERT; withdrawal is planned for Subject 1

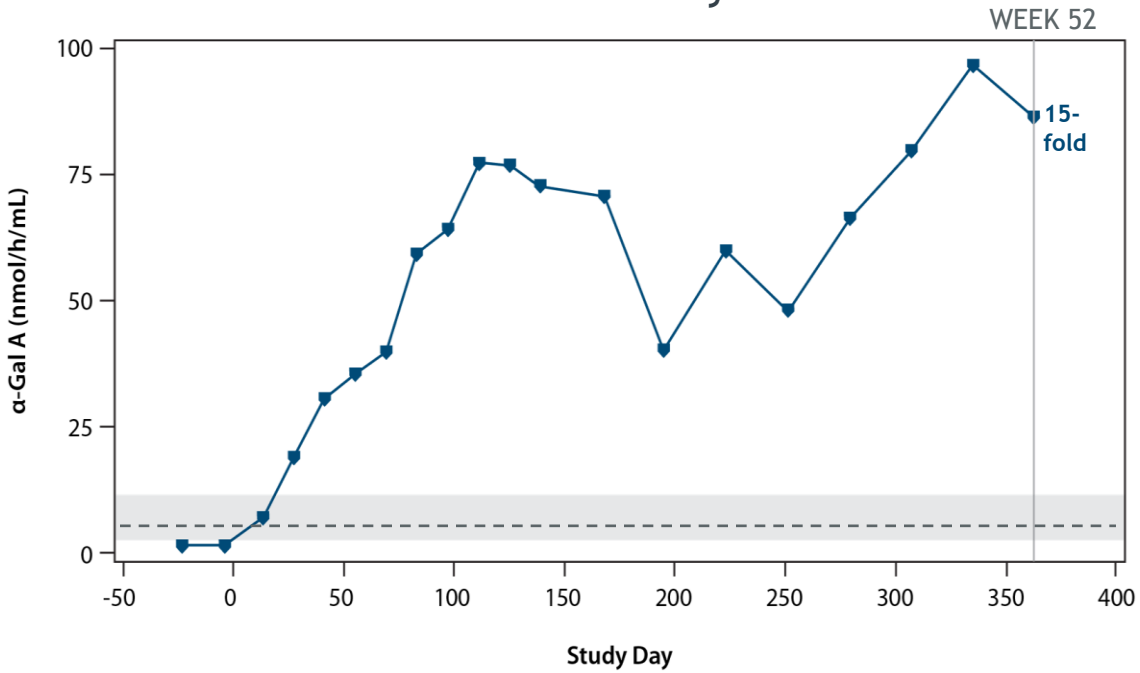
Biomarker results were evaluated from the 4 subjects in dose cohorts 1 and 2 (0.5e13 vg/kg and 1.0e13 vg/kg) as of the cutoff date of November 9, 2021.

*Fold change was calculated at last measured time point. α-Gal A activity was measured using a 3-hour reaction time and is presented in nmol/h/mL. For Subjects 1 and 4, this was sampled at ERT trough. Normal range and mean were determined based on healthy male individuals.
†Subject was withdrawn from ERT at week 24.
ERT, enzyme replacement therapy; vg/kg, vector genomes per kilogram of body weight.

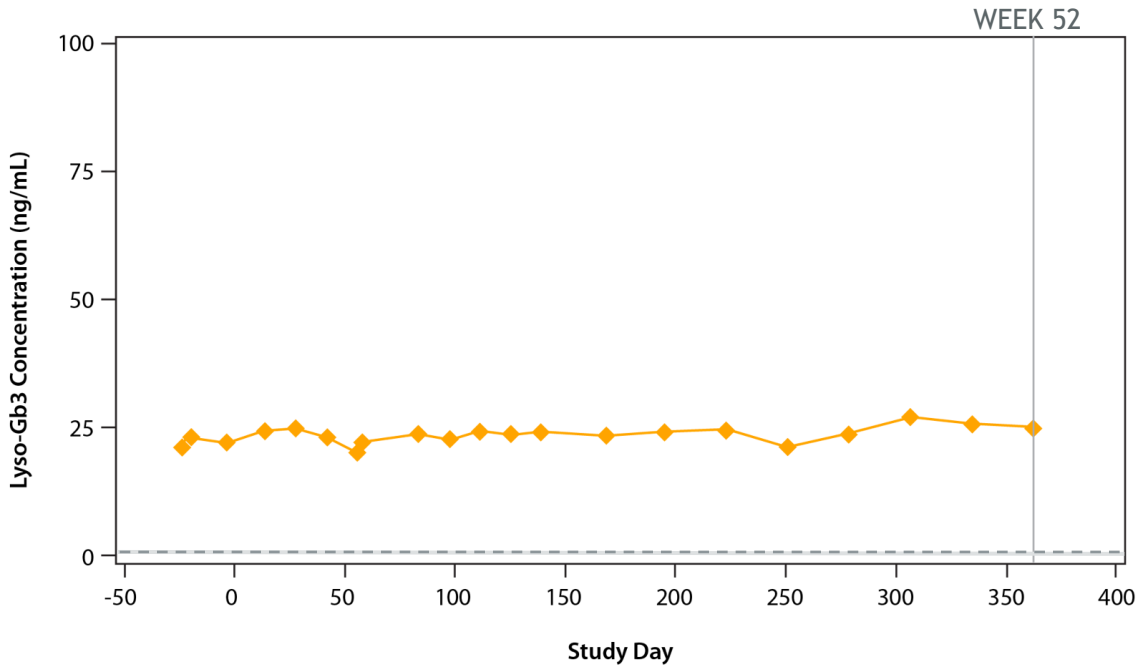
Subject 1: Plasma α-Gal A Activity and Lyso-Gb3

Subject was on ERT and was anti-α-Gal A antibody positive

α-Gal A Activity*



Lyso-Gb3*



- Subject exhibiting above-normal α-Gal A activity that was sustained for 1 year
- Left ventricular hypertrophy on MRI increased in run-in and stabilized following 1 year of treatment

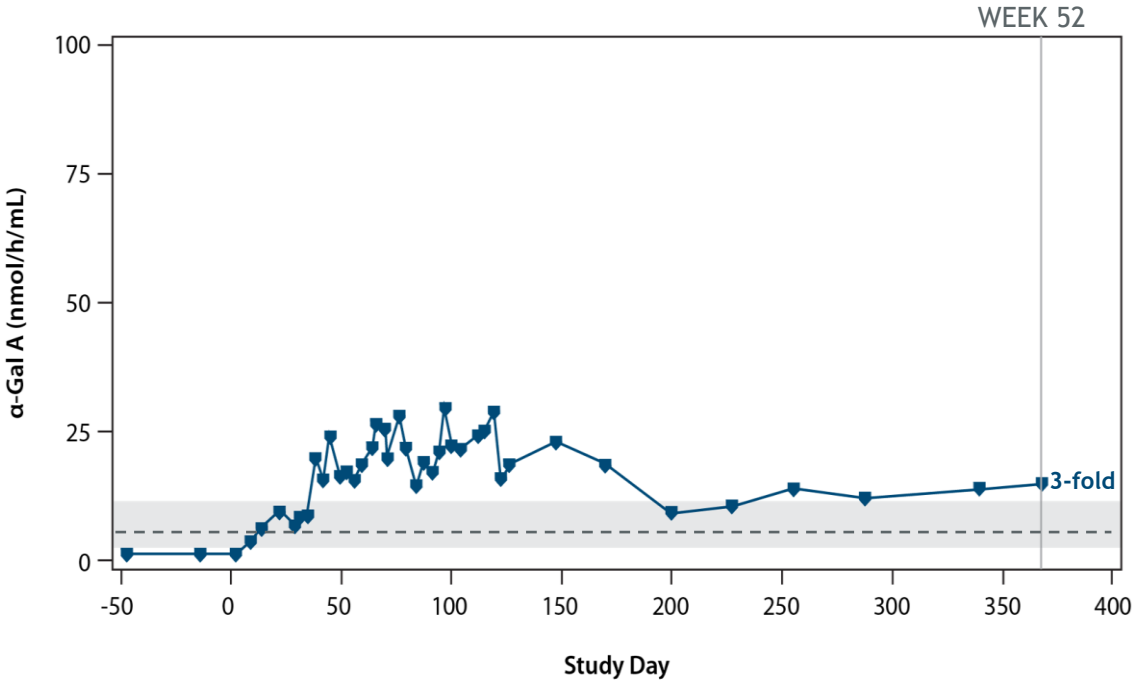
- Low baseline levels of plasma lyso-Gb3 remained steady over time
- Subject reported improvements in leg edema and ability to sweat
- Subject has rolled over into long-term follow-up (follow-up every 3 months for an additional 4 years)

*Only data from ERT trough sample collections (every 2 weeks pre ERT dosing) are shown.
†Normal range and mean were determined based on healthy male individuals.
ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; MRI, magnetic resonance imaging.

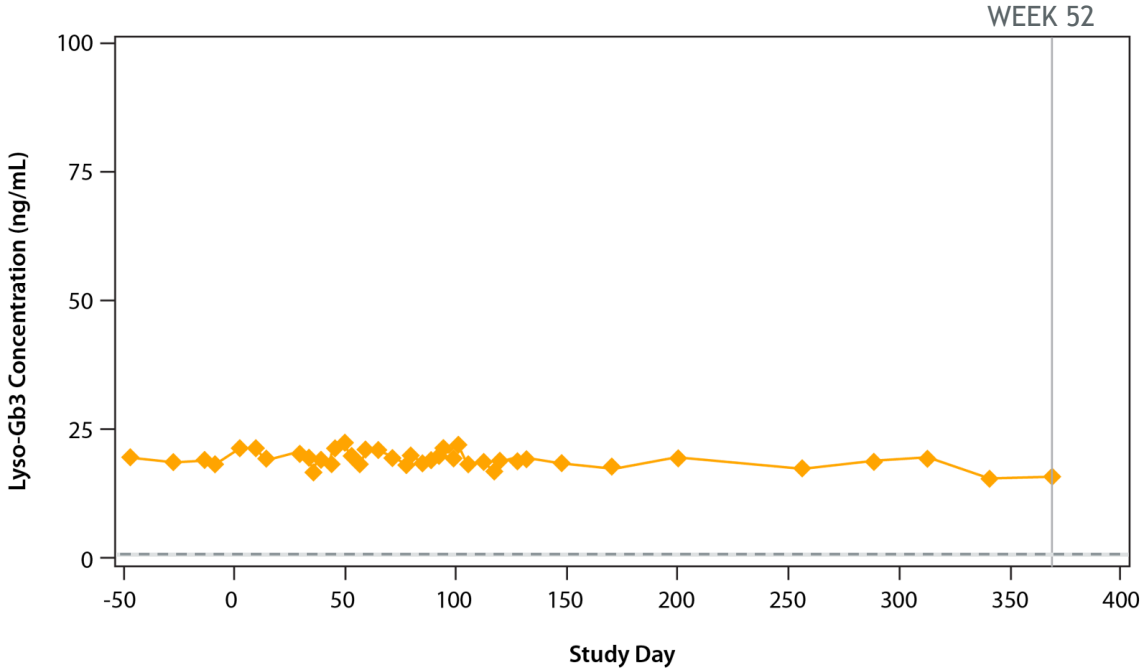
Subject 2: Plasma α-Gal A Activity and Lyso-Gb3

Subject was not on ERT (pseudo-naïve) and was anti-α-Gal A antibody negative

α-Gal A Activity



Lyso-Gb3



- Subject exhibiting above-normal α-Gal A activity that sustained for 1 year
- Subject's baseline mild biventricular dilation improved on MRI at 1 year

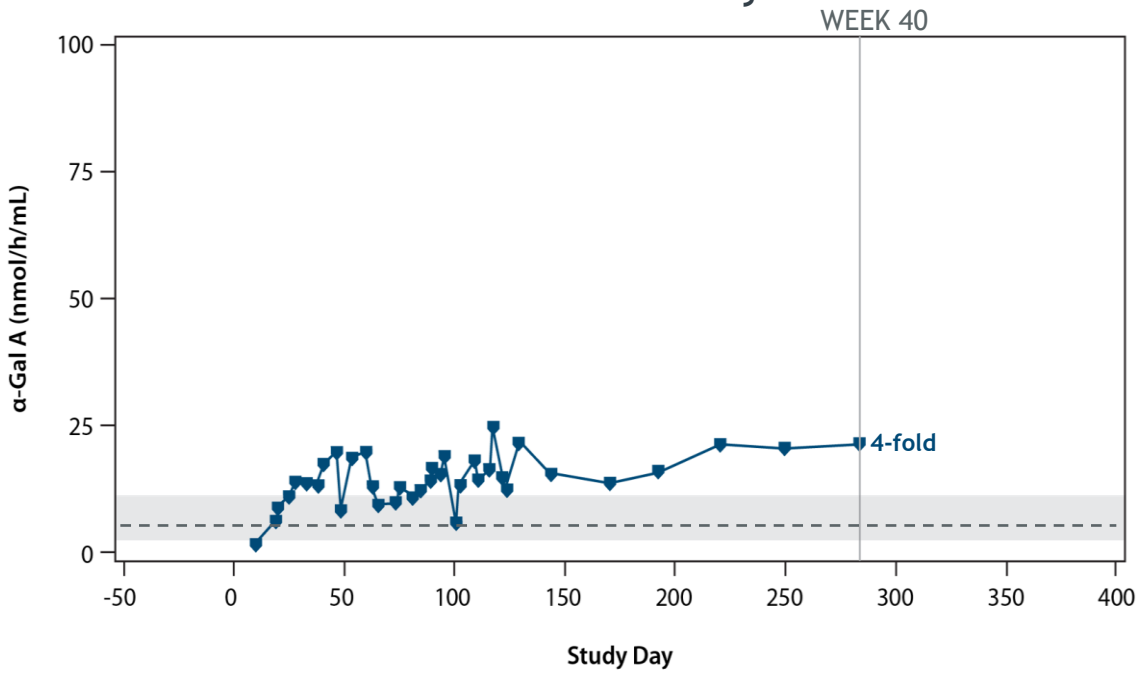
- Low baseline levels of plasma lyso-Gb3 remained steady over time
- Subject reported improvement in ability to sweat
- Subject has rolled over into long-term follow-up (follow-up every 3 months for an additional 4 years)

*Normal range and mean were determined based on healthy male individuals.
ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; MRI, magnetic resonance imaging.

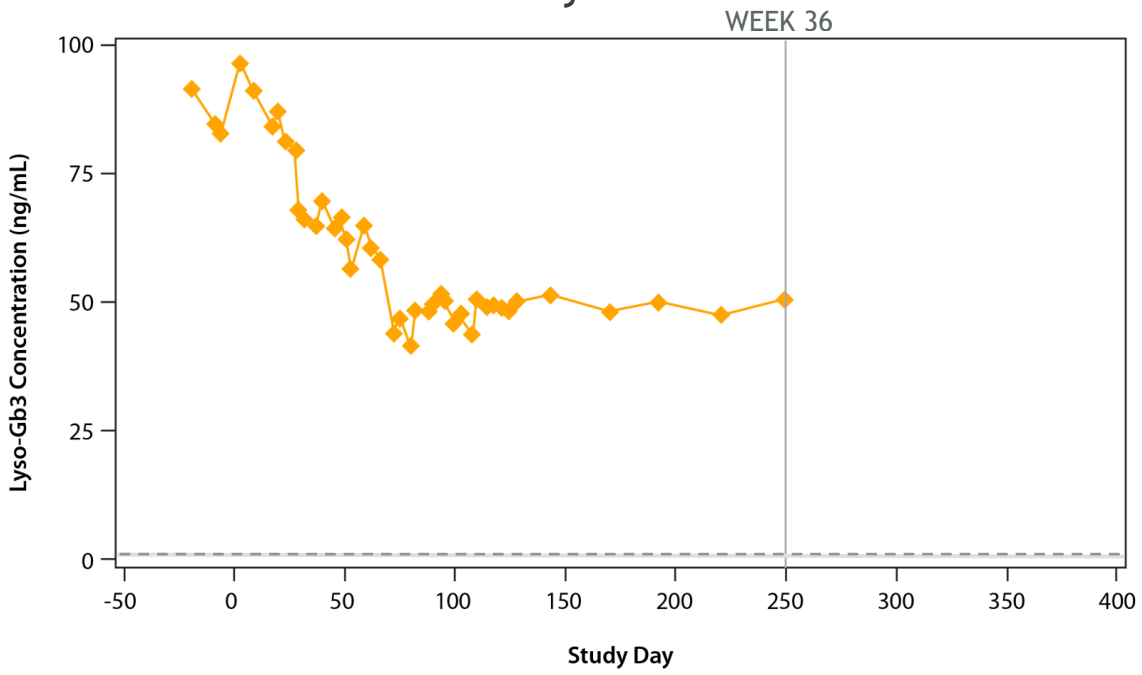
Subject 3: Plasma α-Gal A Activity and Lyso-Gb3

Subject was not on ERT (pseudo-naïve) and was anti-α-Gal A antibody positive

α-Gal A Activity



Lyso-Gb3



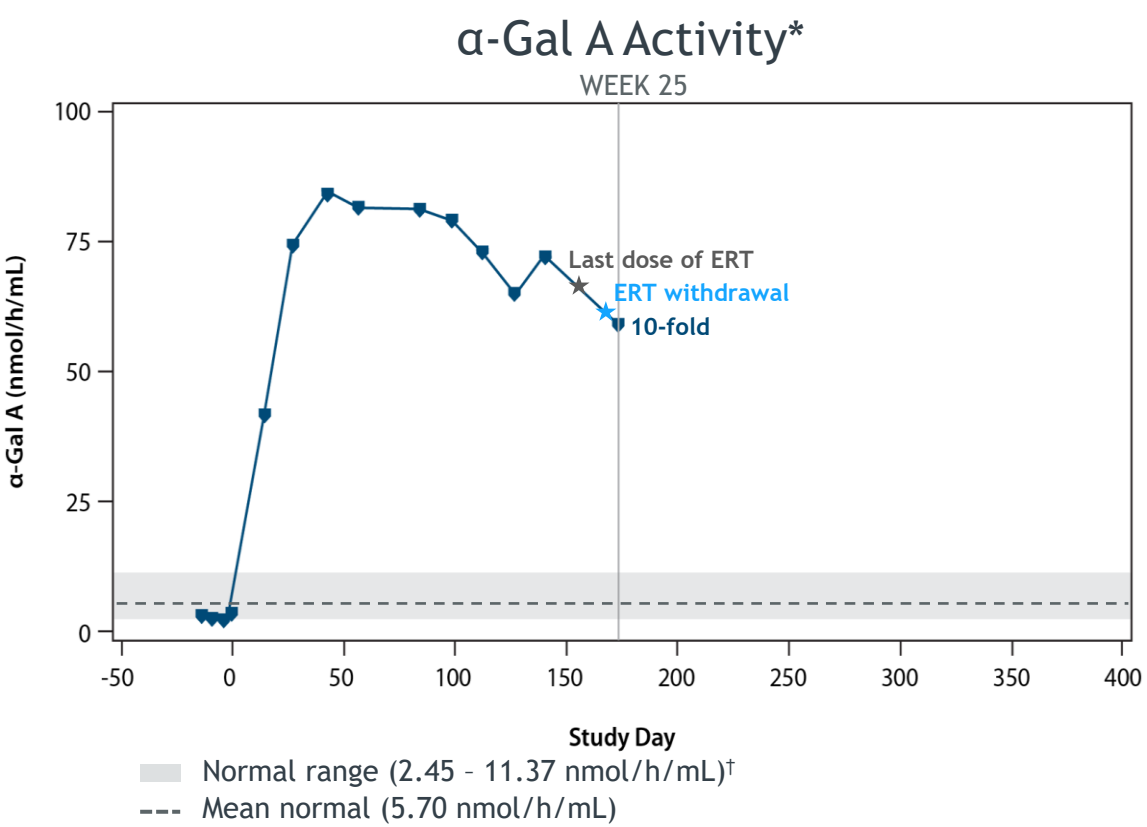
- Subject exhibiting above-normal α-Gal A activity that was sustained up to the last measured point at week 40
- Cardiac MRI was normal at baseline and 24 weeks

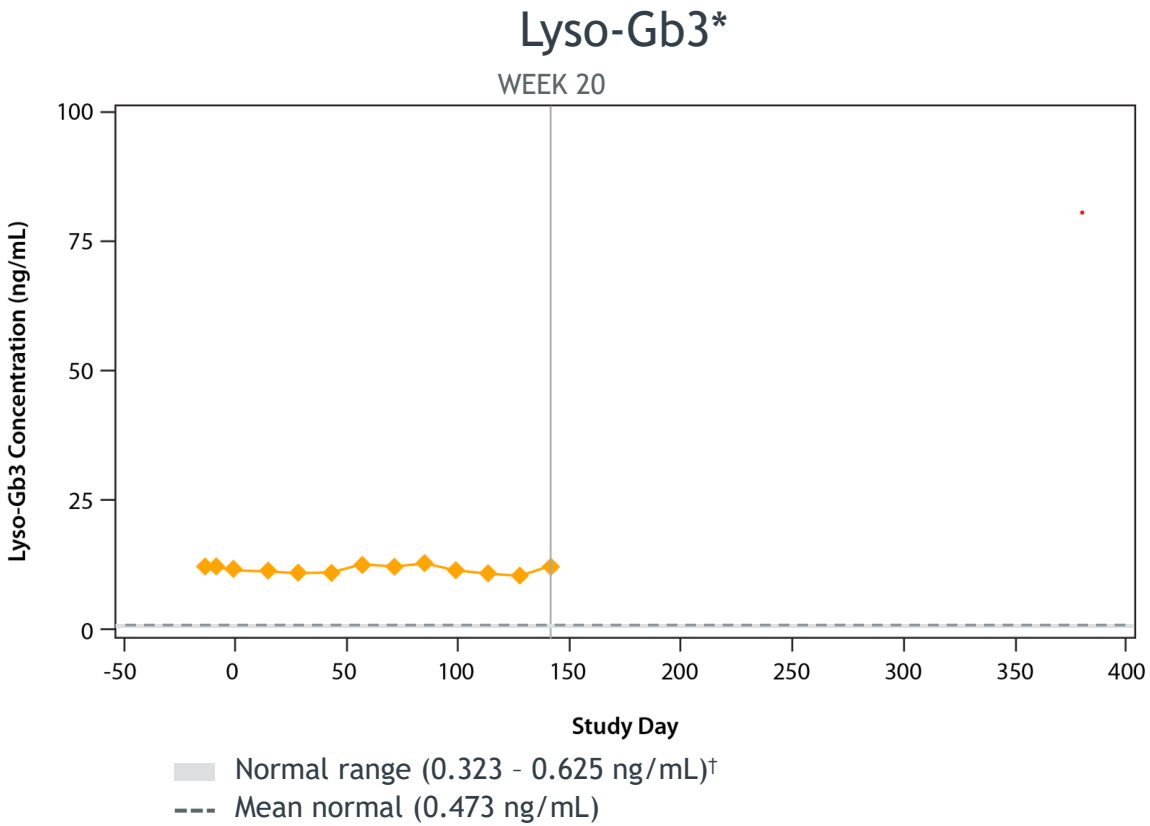
- Subject's plasma lyso-Gb3 levels were elevated at baseline; subject showed ~40% reduction in plasma lyso-Gb3 from baseline within 10 weeks after dosing, maintained through week 36
- Subject reported improvement in ability to sweat

*Normal range and mean were determined based on healthy male individuals.
ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; MRI, magnetic resonance imaging.

Subject 4: Plasma α-Gal A Activity and Lyso-Gb3

Subject was on ERT and was anti-α-Gal A antibody positive





- Subject exhibiting above-normal α-Gal A activity that sustained through 25 weeks
- Cardiac MRI was normal at baseline and 24 weeks

- Low baseline levels of plasma lyso-Gb3 remained steady over time
- Subject was withdrawn from ERT at week 24‡ (last dose of ERT received on study day 155)

*Only data from ERT trough sample collections (every 2 weeks pre ERT dosing) are shown.
†Normal range and mean were determined based on healthy male individuals.
‡Based on 2-week dosing frequency.
ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine; MRI, magnetic resonance imaging.

Conclusions

- Isaralgagene civaparvovec (ST-920) was generally well tolerated; no treatment-related adverse events that were serious or higher than Grade 1 occurred
- Elevated α-Gal A activity was maintained through the last sampling point for all subjects in Cohort 1 and 2, up to 1 year for the first 2 subjects treated who have now begun the long-term follow-up study
- Subject with higher elevation in plasma lyso-Gb3 pre-treatment showed approximately 40% reduction after treatment; subjects with lower baseline levels of plasma lyso-Gb3 maintained steady levels through the latest follow-up date
- Improvements in ability to sweat were reported in the first 3 subjects
- Subject 4 was withdrawn from ERT; withdrawal is planned for Subject 1
- No progression of Fabry cardiomyopathy was observed in Cohort 1 subjects
- STAAR is an ongoing study and based on these data, Phase 3 planning has been initiated

Acknowledgments

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