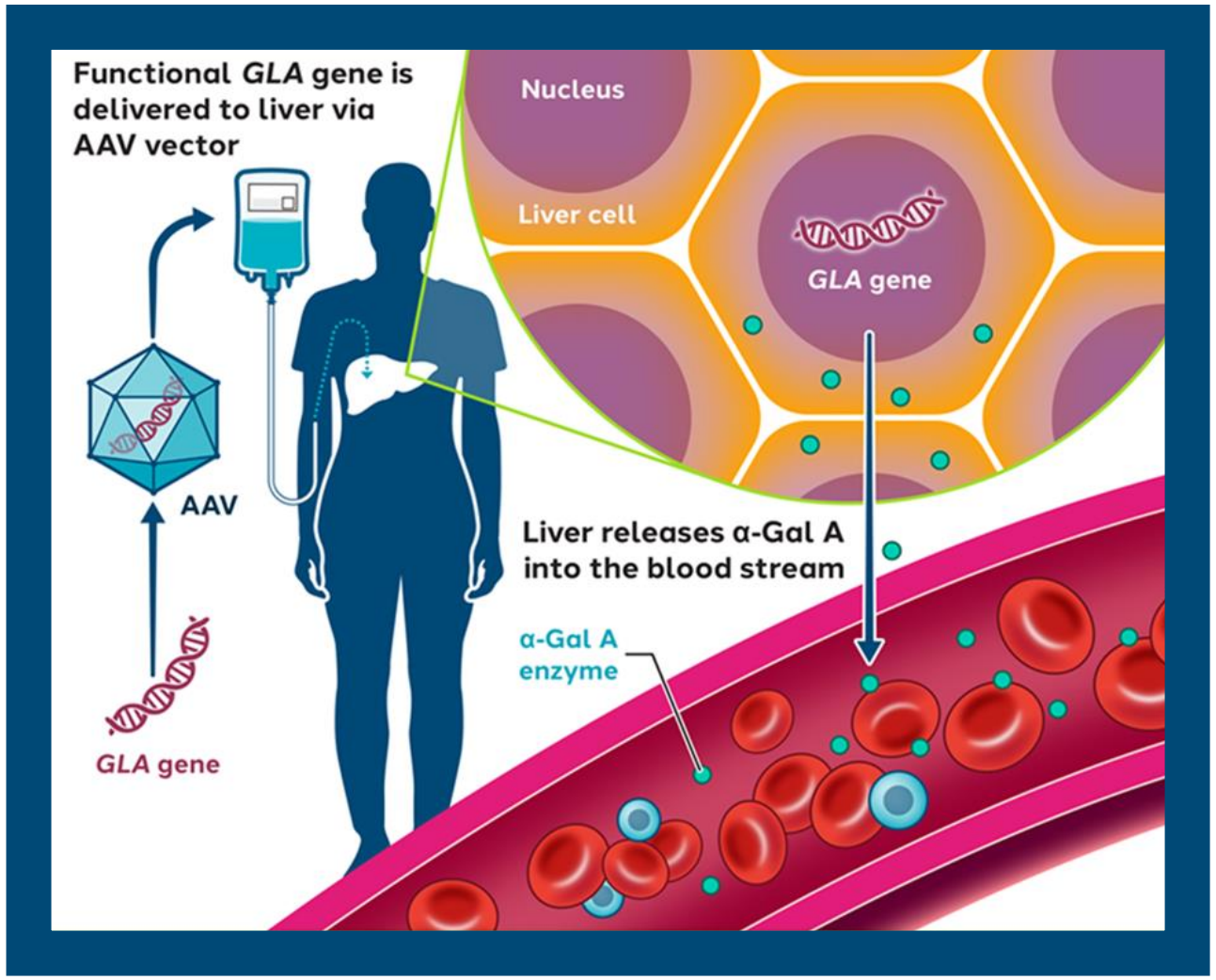
STAAR, a Phase 1/2 study of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease

Robert J. Hopkin[1]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Isaralgagene civaparvovec (ST-920) for Fabry Disease Treatment



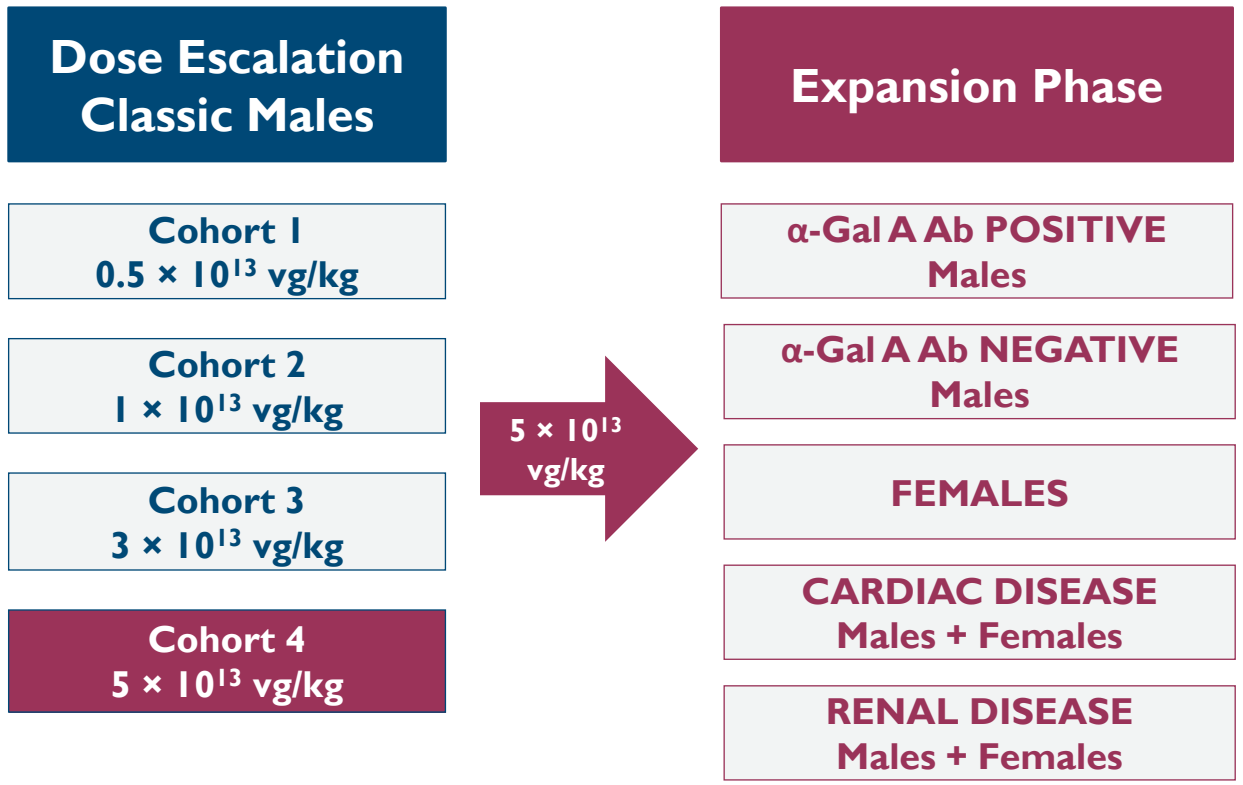
Potential Advantages

- Safe, one-time administration
- Eliminate ERT infusions
- Durable efficacy
- Low immunogenicity
- No prophylaxis with steroids or other immunomodulating agents

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

STAAR phase 1/2 clinical trial overview

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



ENTRY CRITERIA

- Patients ≥18 years of age
  - On ERT Treatment, or
  - ERT-naïve, or
  - ERT-pseudo-naïve (no ERT in prior 6 months)

PRIMARY OBJECTIVE

- Safety and tolerability of ST-920

OTHER KEY OBJECTIVES

- α-Gal A activity and Lyso-Gb3 response
- Discontinuation of ERT
- Preliminary evidence of efficacy
  - Renal function and renal Gb3 inclusions
  - Cardiac function and left ventricular hypertrophy
- Patient Reported Outcomes (Quality of Life)

α-Gal A, alpha galactosidase A; AAV, adeno-associated virus; Ab, antibody; ERT, enzyme replacement therapy; vg/kg, vector genomes per kilogram of total body weight (as assessed by qPCR)

Dose escalation phase: classic Fabry disease males baseline characteristics

vg/kg		Age (years)	ERT	FOS-MSSI Total Max 65.5	General Max 14.5	Neuro Max 15	Cardiac Max 18	Renal Max 18	*GLA* Mutation	Length of Follow up
Cohort 1 0.5×10^{13}	1	48	Agalsidase beta	Moderate 30.5	6.5	7	13	4	G261D	26 M
	2	25	Pseudo naïve	Mild 12	4	8	0	0	T141I	25 M
Cohort 2 1×10^{13}	3	42	Pseudo naïve	Moderate 20.5	8.5	9	3	0	W340R	21 M
	4	22	Agalsidase beta	Mild 10	4	6	0	0	S297Y	17 M
Cohort 3 3×10^{13}	5	39	Agalsidase beta	Moderate 23	5	8	6	4	Q283X	12 M
	6	42	Agalsidase beta	Mild 18.5	8.5	2	8	0	N215S	9 M
	7	51	Agalsidase beta	Severe 40.5	11.5	12	13	4	c.801+ 3A>G	6 M
Cohort 4 5×10^{13}	8	49	Naïve	Moderate 20	2	1	9	8	P362L	6 M
	9	40	Naïve	Mild 18.5	3.5	6	9	0	T141I	6 M

Data cut-off date: October 20, 2022
FOS-MSSI Total Score Classification: Mild ≤18; Moderate (Mod) = 19-38; Severe >38
FOS-MSSI, Fabry Outcome Survey Mainz Severity Score Index; kg, kilogram; M, months; vg, viral genomes

Participants in the dose escalation phase are representative of males with classic Fabry disease

- **Participants generally had mild to moderate disease severity**
  - Mild = 44.4% (4/9)
  - Moderate = 44.4% (4/9)
  - Severe = 11.1% (1/9)
- **Range of organ involvement is variable among participants**
  - Renal involvement present in 44% at baseline (4/9)
  - Cardiac manifestations present at baseline in 78% (7/9)

Expansion phase: baseline characteristics all treated with 5 × 10^{13} vg/kg

				FOS-MSSI						
		Age (years)	ERT	Total Max 65.5	General Max 14.5	Neuro Max 15	Cardiac Max 18	Renal Max 18	*GLA* Mutation	Length of Follow up
Cardiac	12	67 Female	Agalsidase beta	Mild 17.5	5.5	3	9	0	D266N	4 W
α-Gal A Ab Positive Males	10	34	Pseudo naïve	Moderate 32.5	7.5	7	14	4	N34S	10 W
	11	49	Agalsidase beta	Moderate 28	12	9	3	4	Y134S	9W
	13	38	Agalsidase beta	Mild 17.5	6.5	5	6	0	A348Gfs X27 insertion	2 W

- **To date, Expansion Phase participants treated with ST-920 had mild or moderate disease severity**
  - Mild = 50% (2/4)
  - Moderate = 50% (2/4)

Data cut-off date: October 20, 2022
FOS-MSSI Total Score Classification: Mild ≤18; Moderate = 19-38; Severe >38
FOS-MSSI, Fabry Outcome Survey Mainz Severity Score Index; kg, kilogram; vg, viral genomes; W, weeks

ST-920 is generally well tolerated with a favorable safety profile: Overall summary of treatment-emergent AEs

	Dose Escalation Cohorts								Expansion Groups 5×10^{13} vg/kg N = 4		Total N = 13	
	Cohort 1 0.5×10^{13} vg/kg N = 2		Cohort 2 1×10^{13} vg/kg N = 2		Cohort 3 3×10^{13} vg/kg N = 3		Cohort 4 5×10^{13} vg/kg N = 2					
	N	Events	N	Events	N	Events	N	Events	N	Events	N (%)	Events
Adverse Events	2	30	2	20	3	29	2	10	4	18	13 (100%)	107
Treatment Related Adverse Events	1	3	2	3	1	6	2	6	4	12	10 (77%)	30
Serious Adverse Events (Unrelated)	0	0	0	0	1	1	0	0	0	0	1 (7.7%)	1

Most Common Treatment Related Adverse Events (All Grade 1 or Grade 2)

- Pyrexia, headache, chills
- Fabry disease (increased pain)

Serious Adverse Events (Unrelated)

- Unrelated Sepsis (Cohort 3, 1 participant)

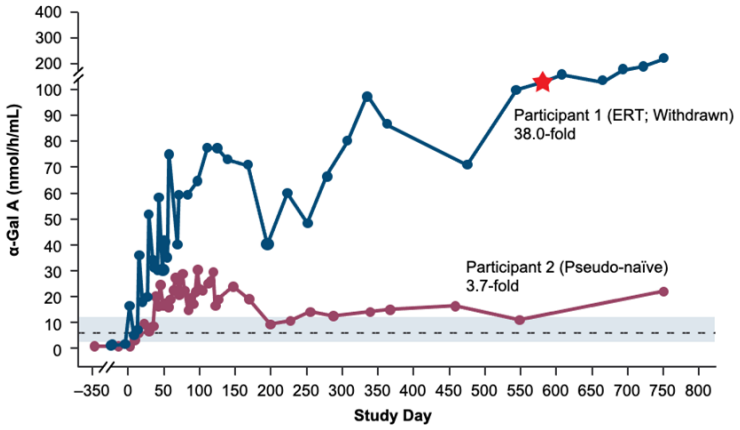
Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms used for adverse event terminology
Data cut-off date: October 20, 2022
Length of follow-up ranged from 2 weeks to 26 months
vg/kg, vector genomes per kilogram of total body weight

No Treatment Related Adverse Events greater than a Grade 2 as of the cut-off date

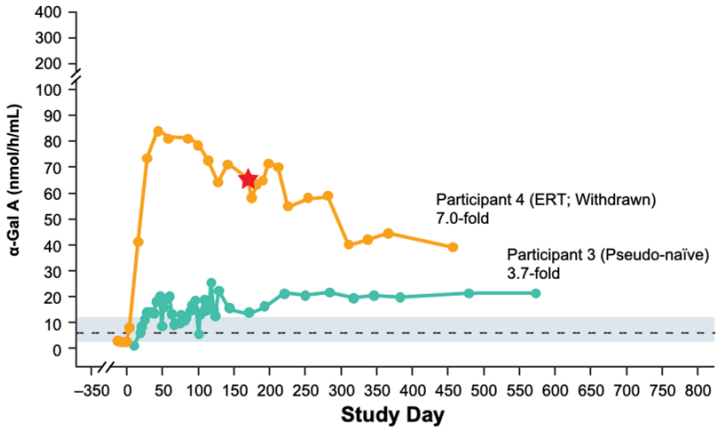
- **Hepatic Enzymes**
  No administration of corticosteroids for transaminase elevations
- **Platelets**
  No clinically significant decreases in platelets observed
- **Cardiac Events**
  Not observed
- **Allergic reaction**
  One expansion phase participant experienced a Grade 1 allergic reaction treated with diphenhydramine

Rapid, predictable and stable expression of α-Gal A activity occurred in all Dose Escalation cohorts

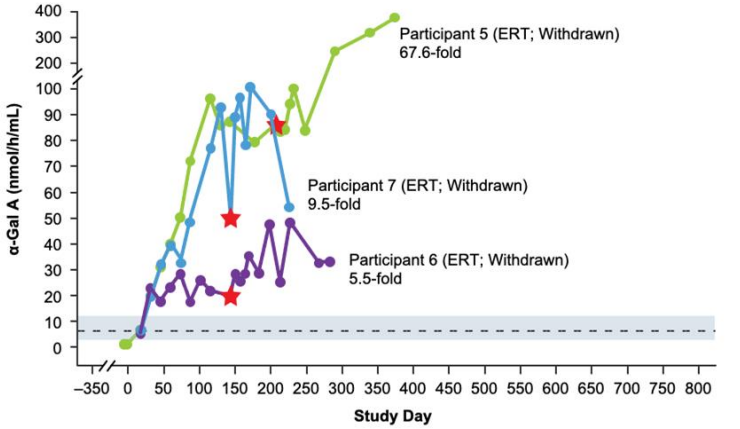
Cohort 1: 0.5 × 10^{13} vg/kg, N = 2



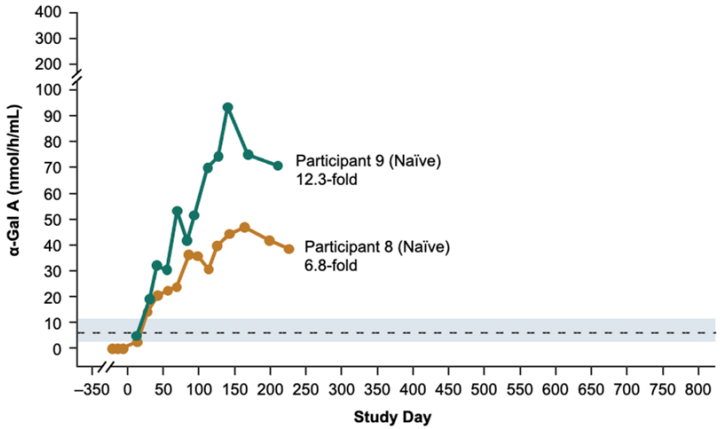
Cohort 2: 1 × 10^{13} vg/kg, N = 2



Cohort 3: 3 × 10^{13} vg/kg, N = 3



Cohort 4: 5 × 10^{13} vg/kg, N = 2

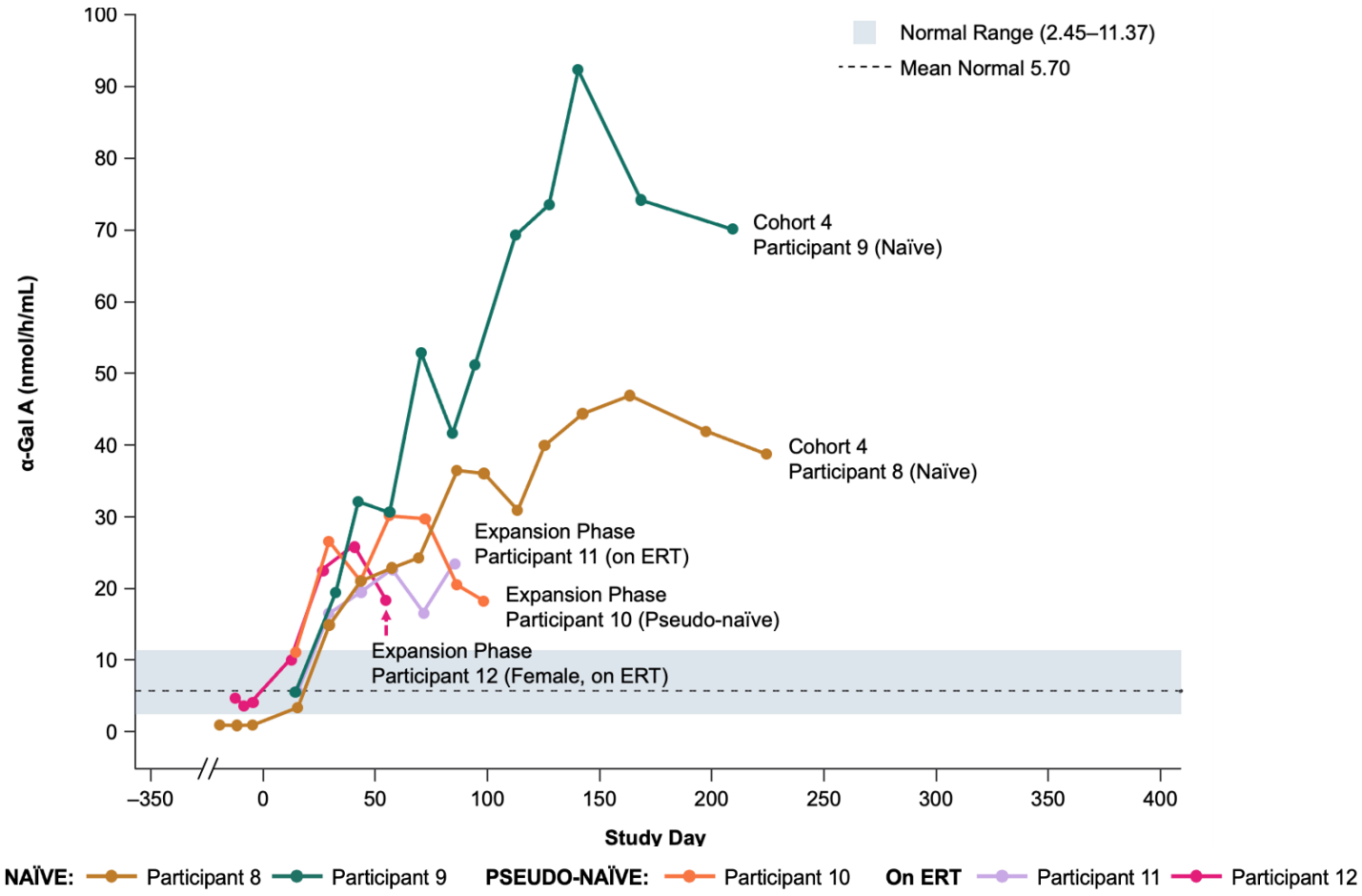


Normal range (2.45 - 11.37) – – – Mean Normal 5.70 ★ ERT Withdrawal

Data cut-off date: November 15, 2022
α-Gal A activity measured using 3-hour reaction time. Normal range determined in healthy males.
Fold change from normal mean was calculated at last measured time point. Long Term Follow-up Data: Data points > Study Day 365.
α-Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy

- Rapid and predictable increase in α-Gal A activity observed in all participants 4-8 weeks after dosing
- Supraphysiological α-Gal A activity maintained in all participants
- ERT withdrawal completed for all 5 participants – with continued supraphysiological activity following withdrawal
- ST-920 expression observed was durable, with α-Gal A activity at supraphysiological levels maintained in all participants, up to more than two years

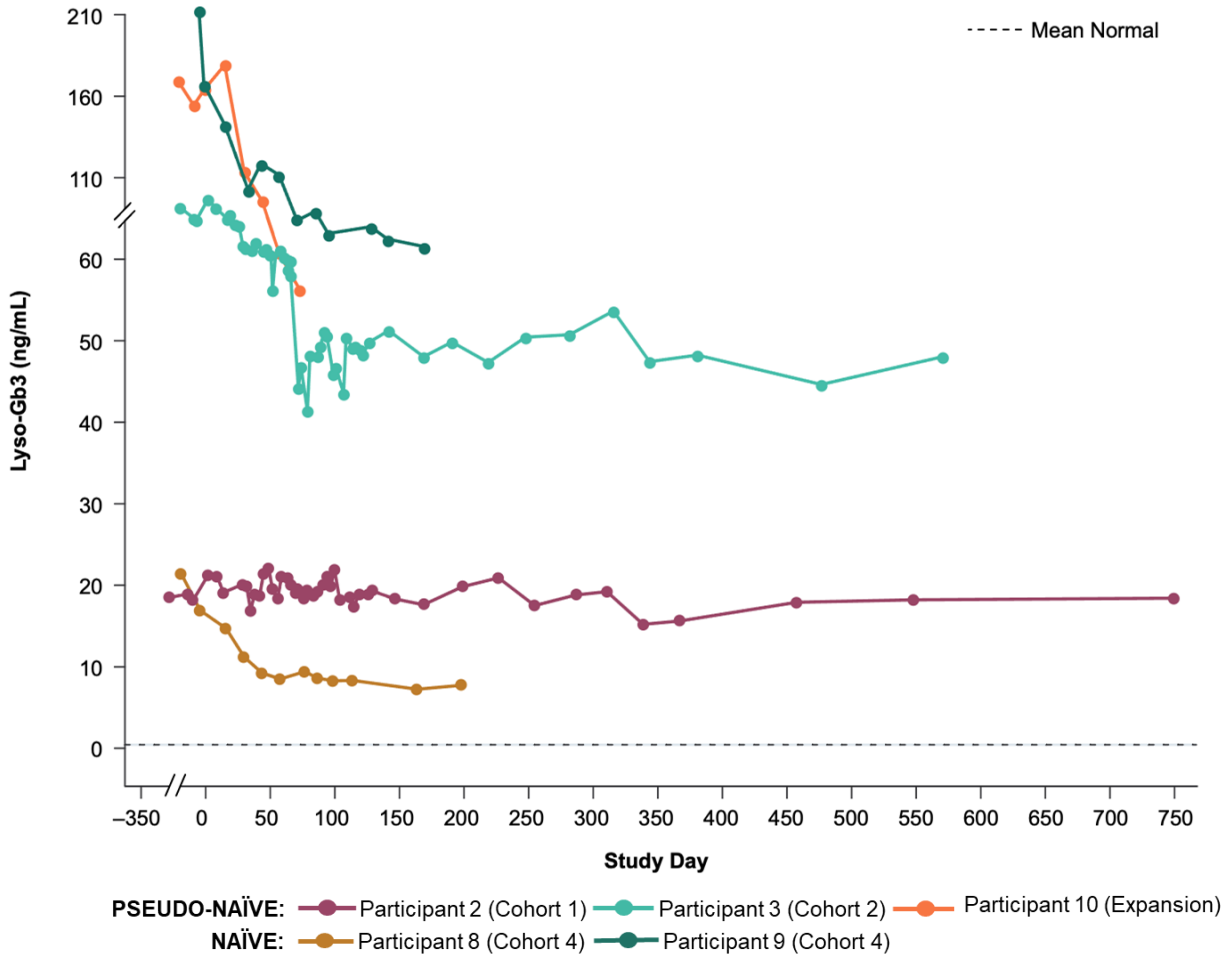
The proposed Phase 3 clinical trial dose (5×10^{13} vg/kg) produced rapid, sustained increases in α-Gal A activity in Dose Escalation (Cohort 4) and Expansion Phase participants



Data cut-off date: November 15, 2022
Participant 13: Week 6: 3.97 nmol/h/mL.
α-Gal A activity measured using 3-hour reaction time. Normal range determined in healthy males.
Long Term Follow-up Data: Data points > Study Day 365
α-Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy

- The highest dose (5×10^{13} vg/kg) produced rapid, predictable and durable increases in plasma α-Gal A activity across all participants as of the data cut-off
- The female participant has demonstrated a similar response profile to males as of the data cut-off

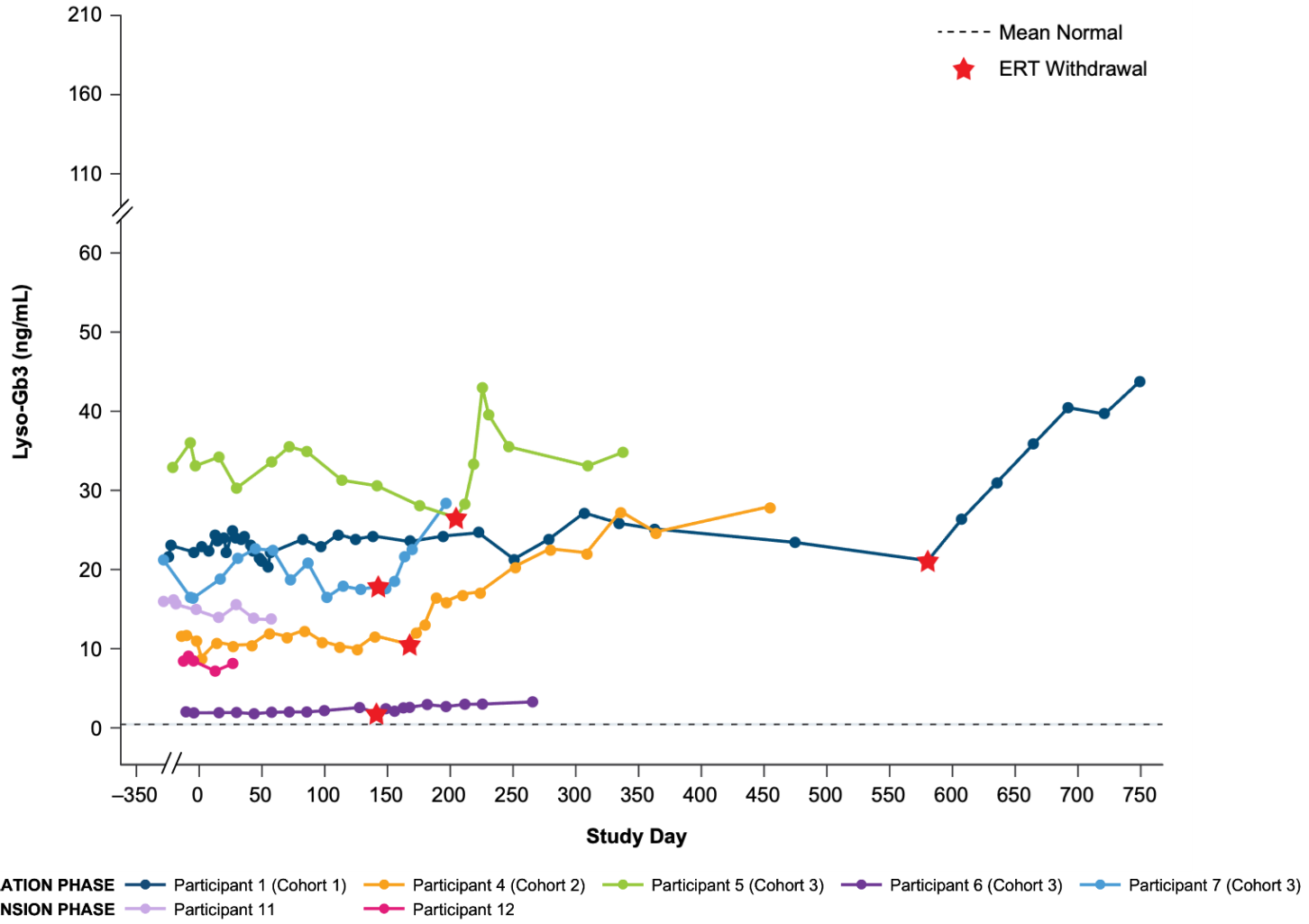
ST-920 effectively lowered plasma Lyso-Gb3 in naïve and pseudo-naïve participants across Dose Escalation and Expansion Phases



Data cut-off date: October 20, 2022
Lyso-Gb3 normal range determined in healthy males and females
Normal range for males and females combined 0.32 to 0.63 ng/mL
*The time point immediately preceding ST-920 administration was presented as the baseline value and used to calculate percent reduction
Long Term Follow-up Data: Data points > Study Day 365
Lyso-Gb3, globotriaosylsphingosine

- Where baseline levels of Lyso-Gb3 started high (>80 ng/mL), participants experienced a 40% to 65%* reduction in plasma levels
- For the first time, at the high dose, we observed a further reduction (54%) in Lyso-Gb3 where baseline plasma levels started lower (<25 ng/mL)
- Plasma Lyso-Gb3 continued to decrease in two participants
- Plasma Lyso-Gb3 levels were stable up to 25 months

Plasma Lyso-Gb3 in ERT-treated dose escalation and expansion phase participants



Data cut-off date: October 20, 2022
Participant 13: Week 2 34.5 ng/mL
Lyso-Gb3 normal range determined in healthy males and females
Normal range for males and females combined 0.32 to 0.63 ng/mL
Long Term Follow-up Data: Data points > Study Day 365
Lyso-Gb3, globotriaosylsphingosine; ERT, enzyme replacement therapy

Dose Escalation Phase

- ERT withdrawal was successful in all ERT-treated participants
- Lyso-Gb3 levels following ERT withdrawal remained within the range of levels and variability normally observed in participants treated with ERT[1, 2, 3]
- In these participants, α-Gal A activity remained elevated, and no participant has experienced symptoms requiring the resumption of ERT

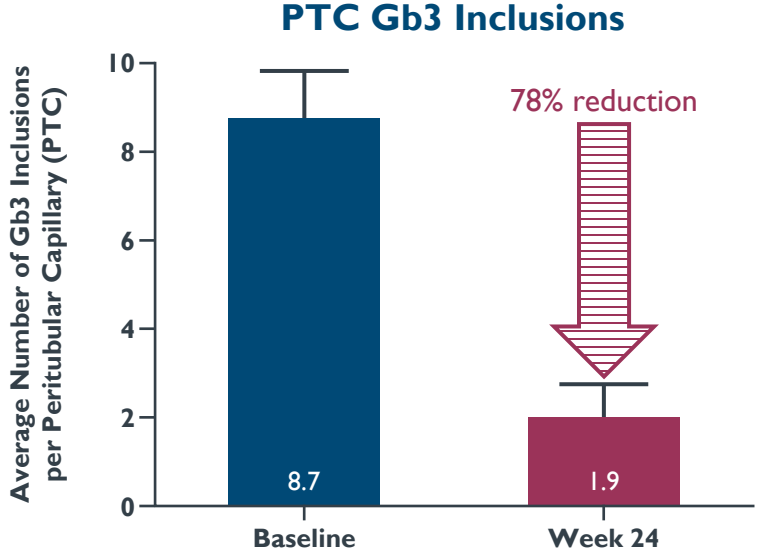
Expansion Phase

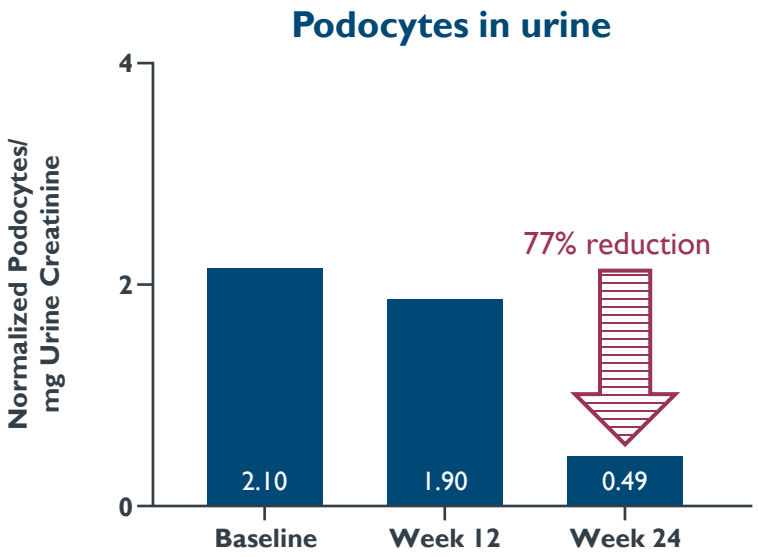
- At this data cut, ERT withdrawal had not yet been initiated for any participant

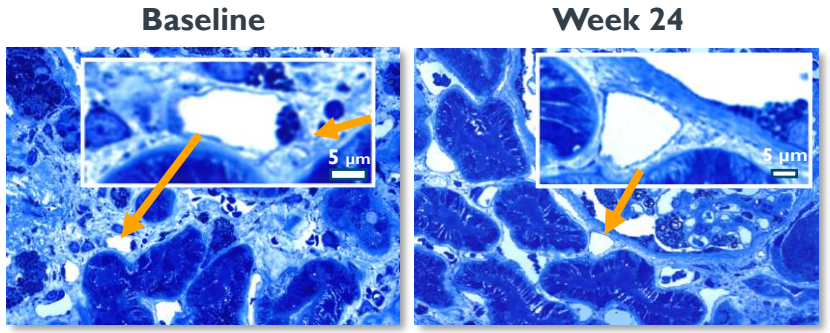
1. Arends, M., M et al. 2018. *J Med Genet*, 55: 351-58.
2. Nowak, A., F. et al. 2022. *J Med Genet*, 59: 287-93.
3. Kramer, J., M. et al. 2018. *Nephrol Dial Transplant*, 33: 1362-72.

Participant 9: biomarkers of nephropathy significantly improved. Reduced renal Gb3 inclusions and podocyturia

Cohort 4 (5×10^{13} vg/kg) - high number of Gb3 inclusions and lyso-Gb3 at baseline







Representative PTC Images

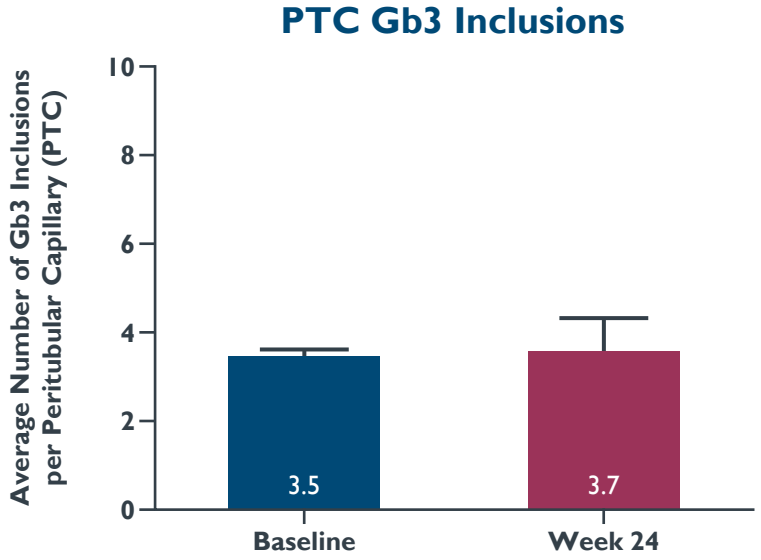
	Baseline	Week 24	Change
Plasma α-Gal A activity (nmol/h/mL)	Below LOQ	74.2	13 × Mean Normal
Plasma lyso-Gb3 (ng/mL)	167	66.8	60% ↓

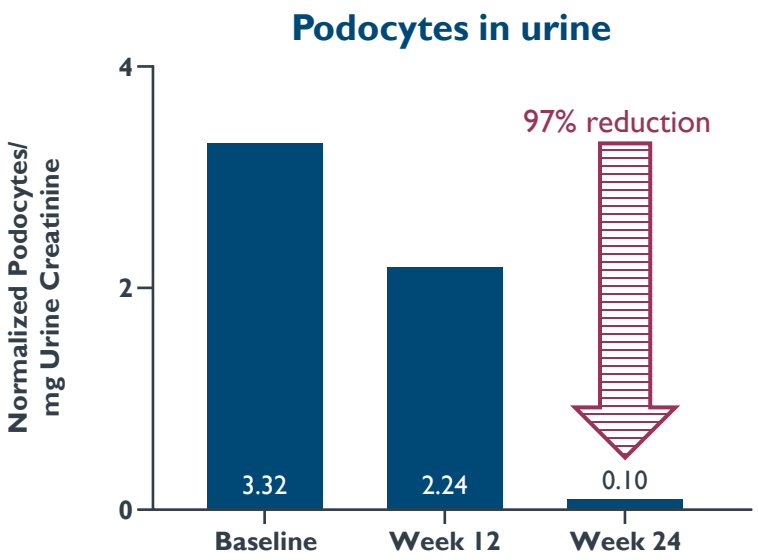
- ST-920 cleared 78% of Gb3 inclusions from peritubular capillaries
- ST-920 also reduced urinary podocyte loss by 77%
- This participant exhibited significant increase in α-Gal A activity and reduction in lyso-Gb3 after dosing with ST-920
- The significant decrease in renal Gb3 inclusions and the reduction in urine podocyte loss support a potential favorable impact on progression of Fabry nephropathy

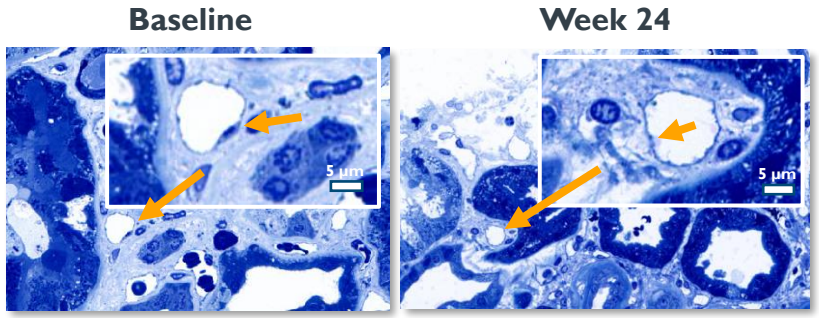
Data cut-off date: October 20, 2022
Podocyte quantification was performed via immunofluorescence with urine creatinine normalization.
The Barisoni Lipid Inclusion Scoring System (BLISS) was used in a blinded manner by 3 independent pathologists to quantify PTC Gb3 inclusions. Lines above the bars indicate standard deviation.
α-Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy; PTC, peritubular capillary; lyso-Gb3, globotriaosylsphingosine; Gb3, globotriaosylceramide

Participant 8: stable renal Gb3 inclusions and reduced podocyturia

Cohort 4 (5×10^{13} vg/kg) - lower number of Gb3 inclusions and lyso-Gb3 at baseline







Representative PTC Images

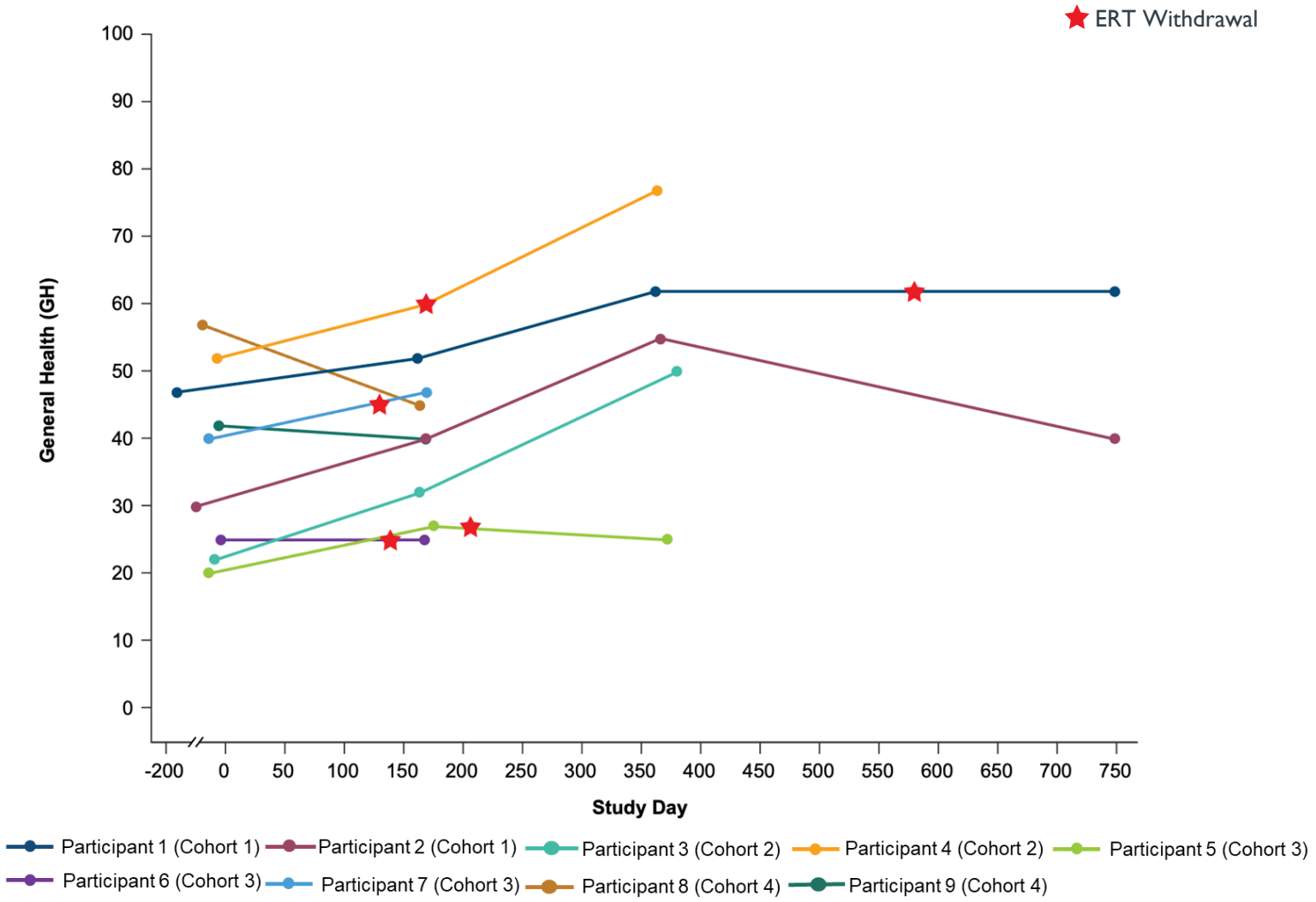
	Baseline	Week 24	Change
Plasma α-Gal A activity (nmol/h/mL)	0.96	46.89	8 × mean normal
Plasma lyso-Gb3 (ng/mL)	16.9	7.24	57% ↓

- Peritubular capillary (PTC) renal Gb3 inclusions were stable in this participant
- ST-920 reduced urinary podocyte loss by 97%
- This participant exhibited significant increases in α-Gal A activity and reductions in lyso-Gb3 after dosing with ST-920
- These data provide additional evidence of a potentially favorable effect on Fabry nephropathy

In this participant chronic kidney disease may be multifactorial with possible contributions from hypertension and type 2 diabetes

Data cut-off date: October 20, 2022
Podocyte quantification was performed via immunofluorescence with urine creatinine normalization.
The Barisoni Lipid Inclusion Scoring System (BLISS) was used in a blinded manner by 3 independent pathologists to quantify PTC Gb3 inclusions. Lines above the bars indicate standard deviation.
α-Gal A, alpha-galactosidase A; ERT, enzyme replacement therapy; PTC, peritubular capillary; lyso-Gb3, globotriaosylsphingosine; Gb3, globotriaosylceramide

Dose escalation phase: clinically meaningful and statistically significant increase in mean SF-36 general health scores



Data cut-off date: October 20, 2022
Long Term Follow-up Data: Data points > Study Day 365
SF-36, Short Form-36

General Health Score Dose Escalation Phase

Study Week	Change from Baseline Mean ± SE, 95% CL
Baseline	- - -
Week 24 (n=8)	2.9±2.57 [-3.2, 8.9] p=0.2996
Week 52 (n = 5)	**19.6±4.26 [7.8, 31.4] p=0.010**

Reference: ADQS, Listing 16.2.14, Table 14.3.4.5a
Data points from the LTFU (Day 750) are not included
CL: Confidence limit; SE, standard error

- Change from baseline at Week 52 is statistically significant with mean=19.6, 95% CL: [7.8, 31.4], p=0.010 (paired t-test)
- A 3-to-5-point change on any SF-36 score is the minimally clinically important difference (MCID)[1]

1. Arends, M., C. E. Hollak, and M. Biegstraaten. 2015. *Orphanet J Rare Dis*, 10: 77.

Conclusion | Isaralgagene civaparvovec (ST-920)

EVIDENCE OF EFFICACY IN FABRY DISEASE

- Clearance or stabilization of renal Gb3 inclusions along with reductions in urine podocyte loss suggest a favorable impact on progression of Fabry nephropathy
- Stable expression of α–Galactosidase A activity in 13 participants for over two years for the longest treated participant
- All participants in the Dose Escalation phase who commenced the study on ERT have been successfully withdrawn from ERT and remain off ERT with sustained supraphysiological levels of α–Galactosidase A activity
- 40% to 65% plasma Lyso-Gb3 reduction in naïve/pseudo-naïve participants with high plasma Lyso-Gb3
- Lyso-Gb3 levels following ERT withdrawal remained within the range of levels and variability normally observed in participants treated with ERT
- Clinically meaningful and statistically significant increase in mean general health scores

FAVORABLE SAFETY PROFILE TO DATE

- Generally well tolerated at all doses (0.5×10^{13} to 5×10^{13} vg/kg)
  - Classic males (n=12) and a female (n=1)
  - ERT-treated and ERT-naïve participants

LOW AAV2/6 CAPSID IMMUNOGENICITY

- No requirement for prophylactic corticosteroids or other immune modulating agents

THE PROPOSED PHASE 3 STUDY DOSE IS 5×10^{13} VG/KG

- The Phase 1/2 STAAR study Expansion Phase is ongoing, with a further four participants dosed since the October 20, 2022 cut-off date. Phase 3 preparation is in progress.

Acknowledgments

Study authors: Robert J. Hopkin[1], Jaya Ganesh[2], Patrick Deegan[3], Ozlem Goker-Alpan[4], John Bernat[5], William R. Wilcox[6], Madeleine V. Pahl[7], Chester B. Whitley[8], Derralynn Hughes[9], Kathleen Nicholls[10], Liching Cao[11], Michael Chen[11], Lisa H. Shiue[11], Emma Bowden[11], Sravan Jaggumantri[11], Cristobal Passalacqua[11], Bernard Souberbielle[11], John Shoffner[11], Matthew Meriggioli[11], Bettina M. Cockroft[11].

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA,
[2]The Icahn School of Medicine at Mount Sinai, New York, NY, USA,
[3]Addenbrooke's Hospital, Cambridge, United Kingdom,
[4]Lysosomal & Rare Disorders Research & Treatment Center, Inc, Fairfax, VA, USA,
[5]University of Iowa, Iowa City, IA, USA,
[6]Human Genetics, Emory University, Atlanta, GA, USA,
[7]University of California, Irvine, Orange, CA, USA,
[8]University of Minnesota, Minneapolis, MN, USA,
[9]University College London, London, United Kingdom,
[10]Royal Melbourne Hospital, Parkville, Australia,
[11]Sangamo Therapeutics, Inc., Brisbane, CA, USA.

The authors would like to thank the patients, families, study investigators and their teams for their participation in this study