Isaralgagene civaparvovec (ST-920) gene therapy for adults with Fabry disease: Pharmacology and immunogenicity outcomes from the Phase 1/2 STAAR study and ongoing long-term follow-up

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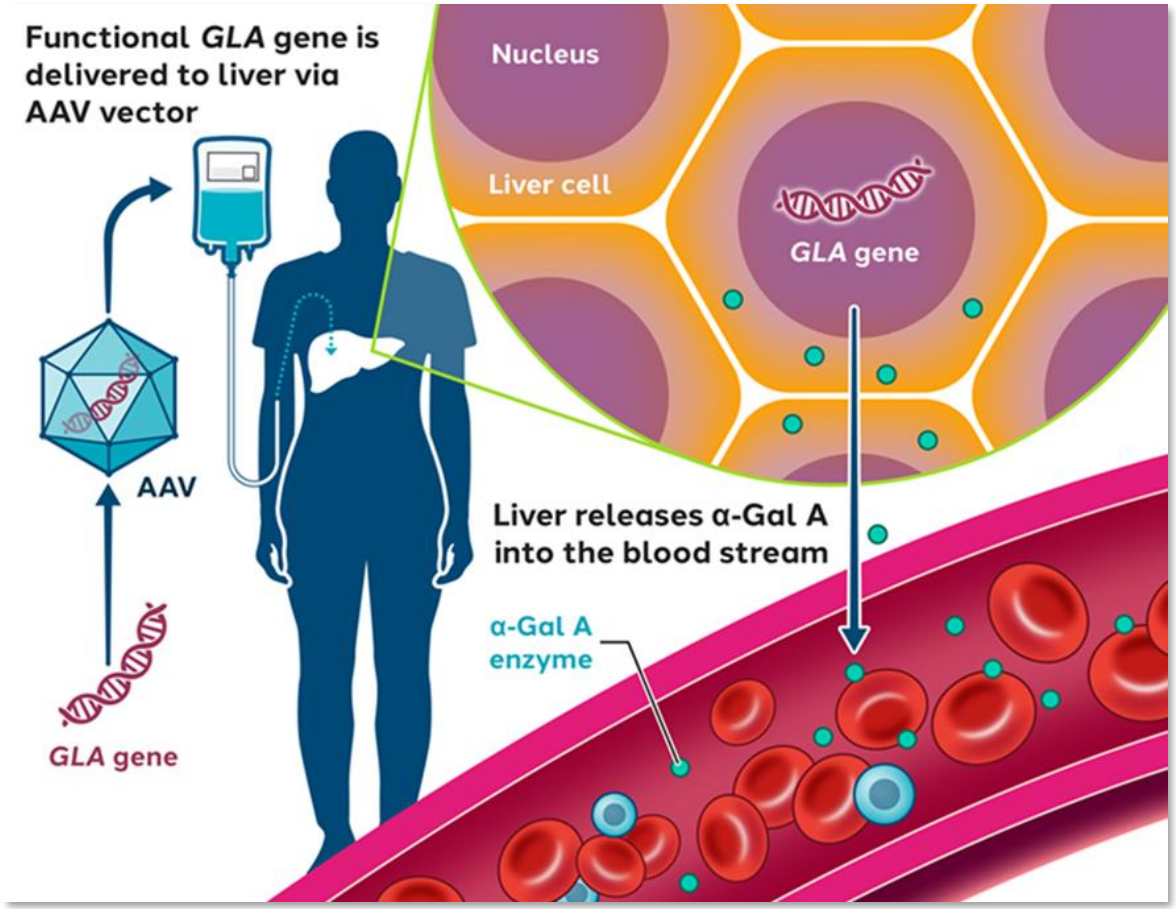
ST-920 employs a recombinant AAV2/6 vector with human *GLA* cDNA for continuous, liver-specific α-Gal-A expression



Indication

- Fabry disease

Mechanism

- Transduced liver cells produce and secrete functional α-Gal A into the bloodstream
- α-Gal A is taken up by peripheral tissues to reduce Gb3 and lyso-Gb3 substrates

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; globotriaosylceramide, Gb3; globotriaosylsphingosine, lyso-Gb3

STAAR Phase 1/2 clinical study overview

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

Long-term follow-up of subjects who were treated with ST-920 (ST-920-LT01, NCT05039866) - 10Apr2025 data cut-off

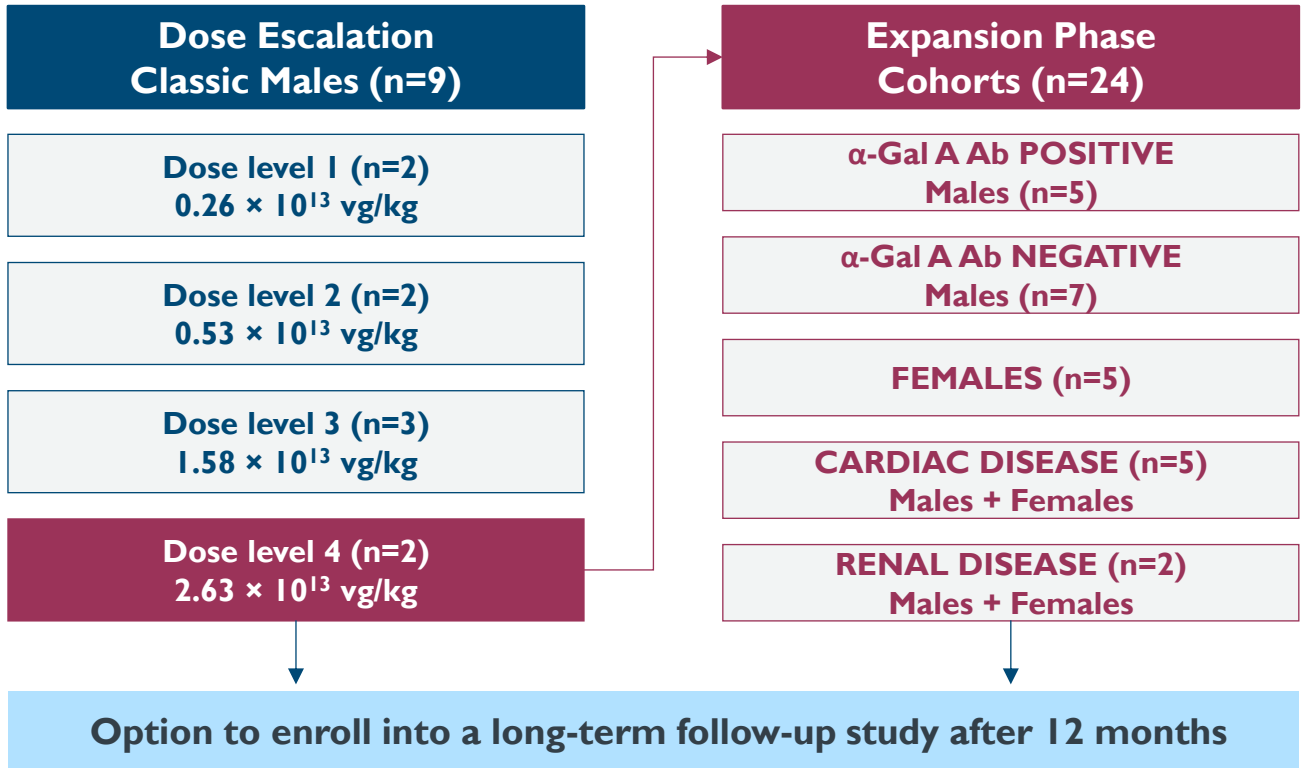
Median duration of post-infusion follow-up is 25.07 months, ranging from 4.9 to 54.3 months

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

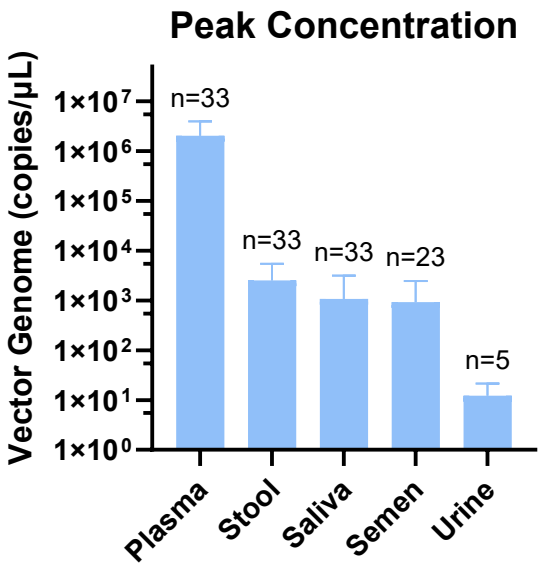
Main objectives

- Safety and tolerability of ST-920
- Vector DNA shedding
- 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

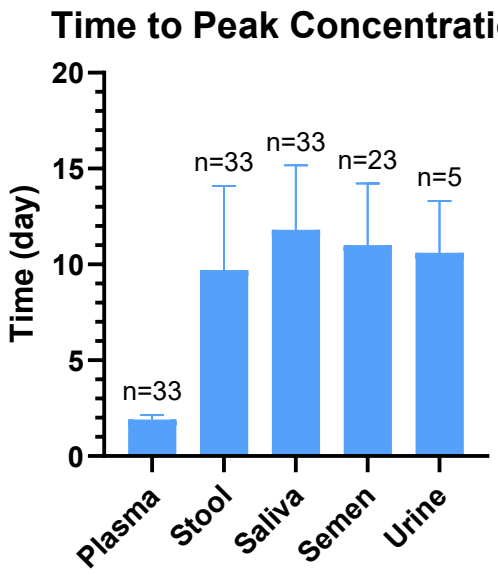


α-Gal A, alpha galactosidase A; AAV, adeno-associated virus; Ab, antibody; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; Lyso-Gb3, globotriaosylsphingosine; vg/kg, vector genomes per kilogram of total body weight (as assessed by digital droplet PCR [ddPCR])

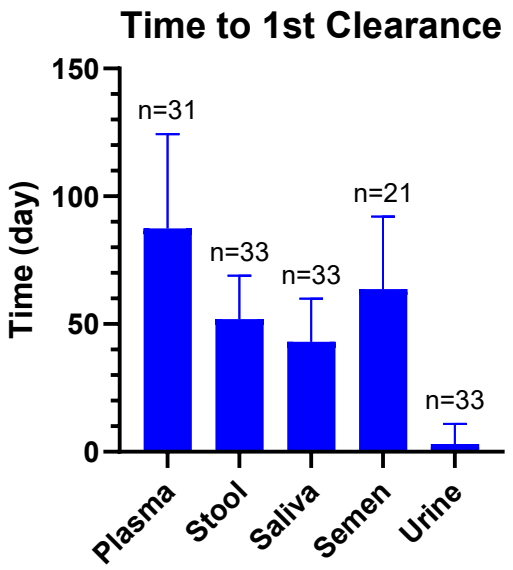
ST-920 vector DNA fully cleared from shedding matrices



Peak vector genome concentrations were highest in plasma and lowest in urine



Time to peak concentration ranged from 1.9 (plasma) to 11.8 (saliva) days



Clearance time (day) (low to high):

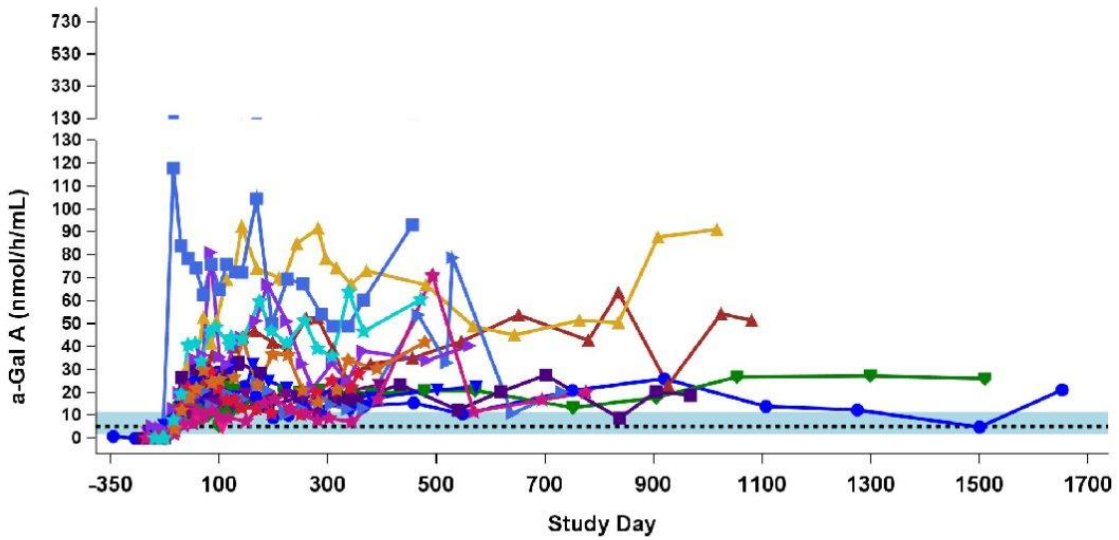
Urine (3.1), saliva, stool, semen and plasma (87.4)

Data cut-off date: 10 April 2025

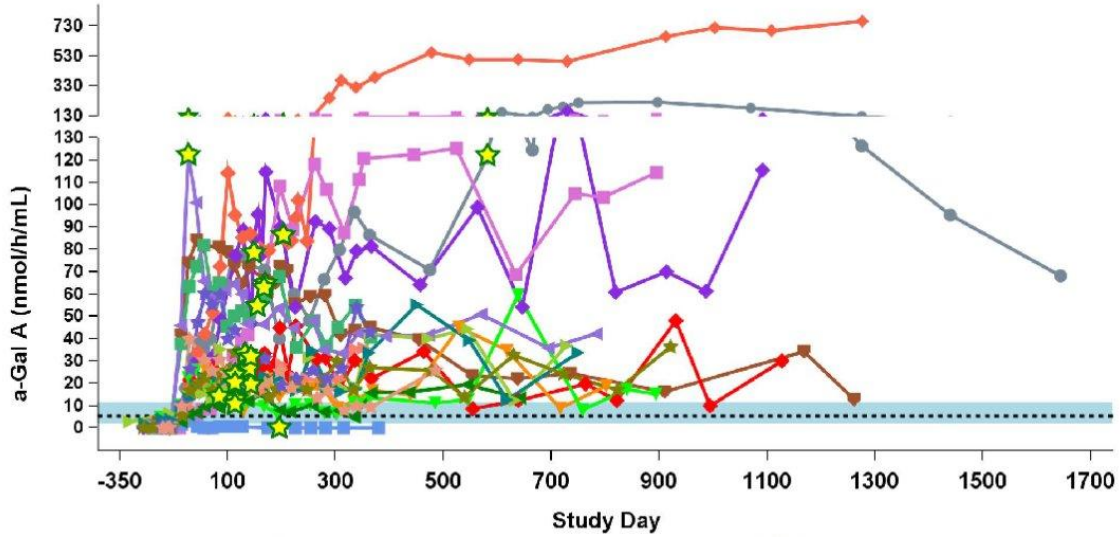
Sustained supraphysiological plasma α-Gal A activity

- 32/33 participants (97.0%) maintained physiological plasma α-Gal A activity levels (≥1.99 nmol/h/mL)
- 31/33 participants (93.9%) maintained supraphysiological plasma α-Gal A activity levels (≥11.37 nmol/h/mL)
- The median time reaching physiological and supraphysiological levels was 30.0 days (range: 2 to 97 days)
- A general dose response observed in ERT naïve/pseudo-naïve participants

ERT Naïve/Pseudo-naïve (n=15)



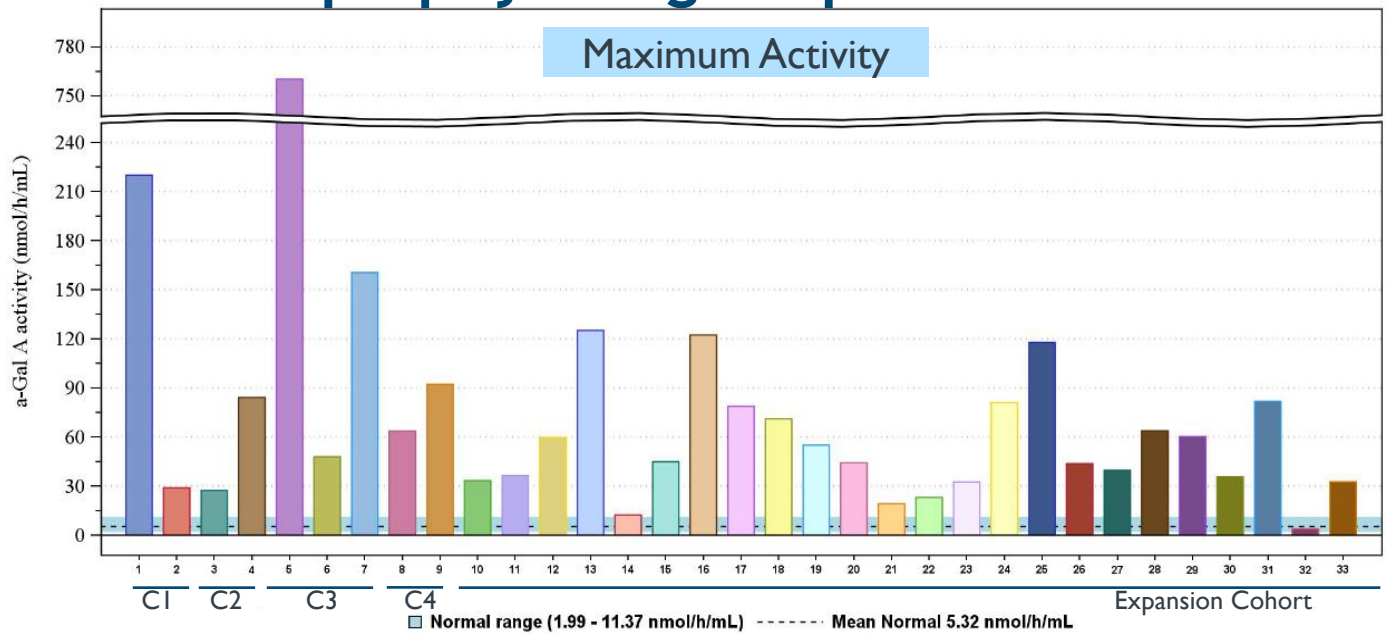
ERT Experienced (n=18)*

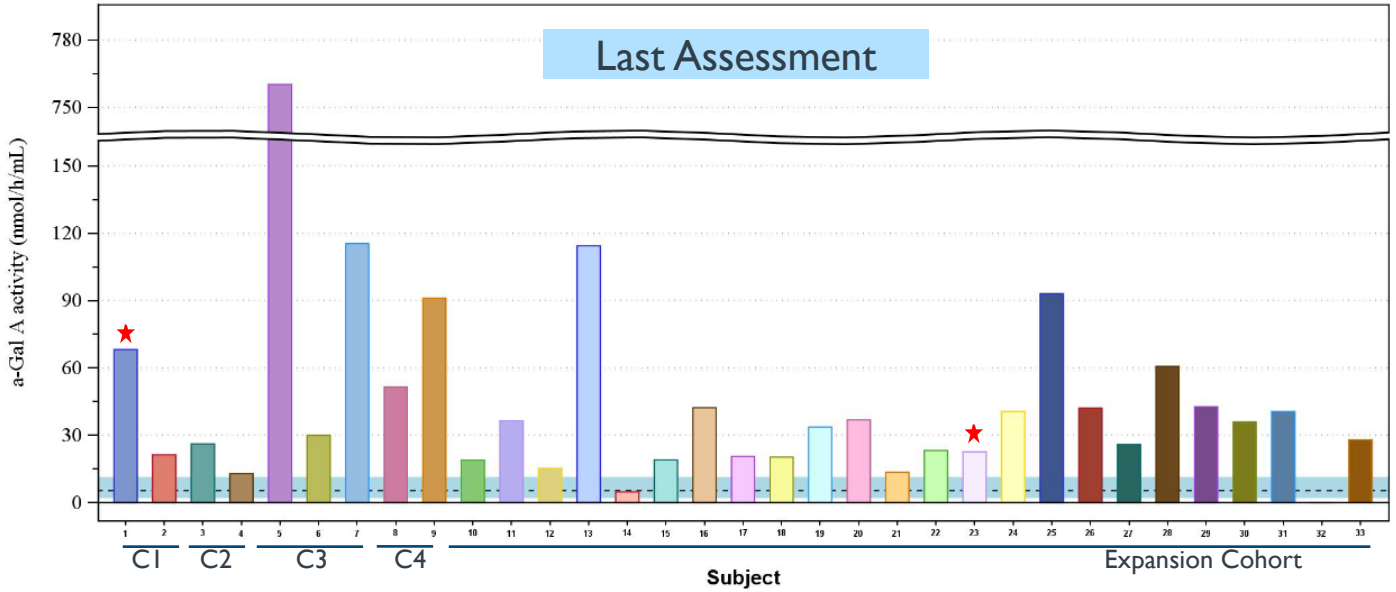


** Samples were collected at ERT trough*

Data cut-off date: 10 April 2025
α-Gal A, alpha galactosidase A; ERT, enzyme replacement therapy

Sustained supraphysiological plasma α-Gal A activity





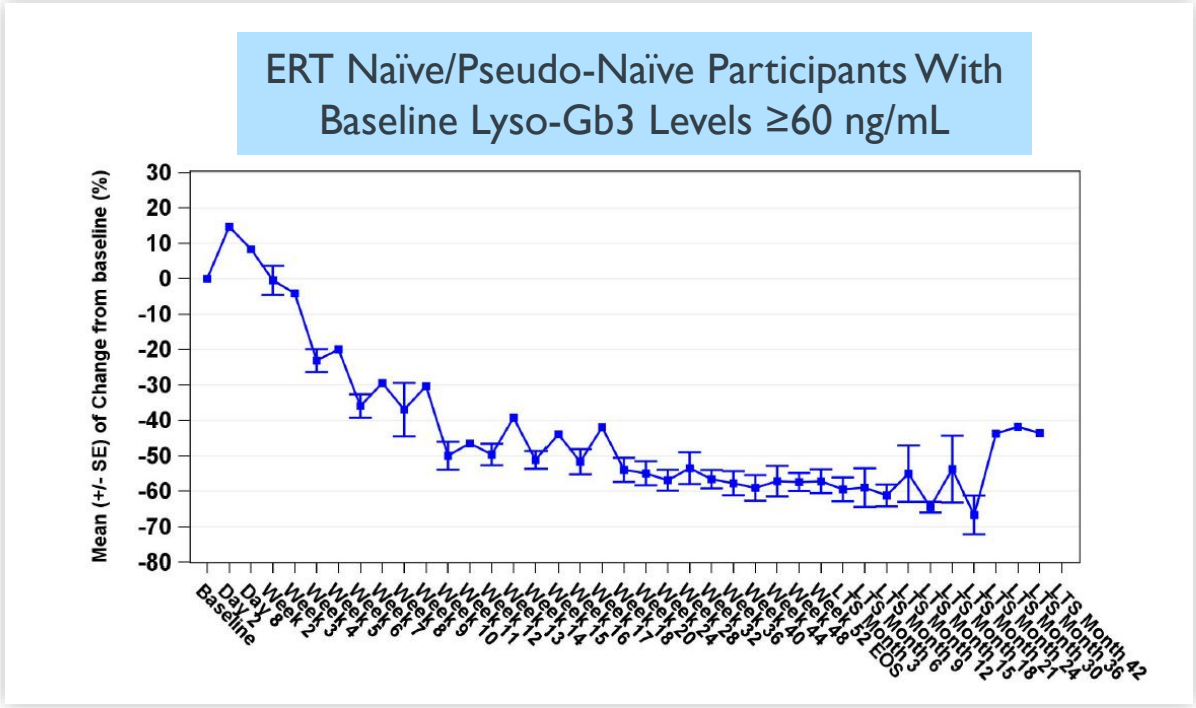
Data cut-off date: 10 April 2025

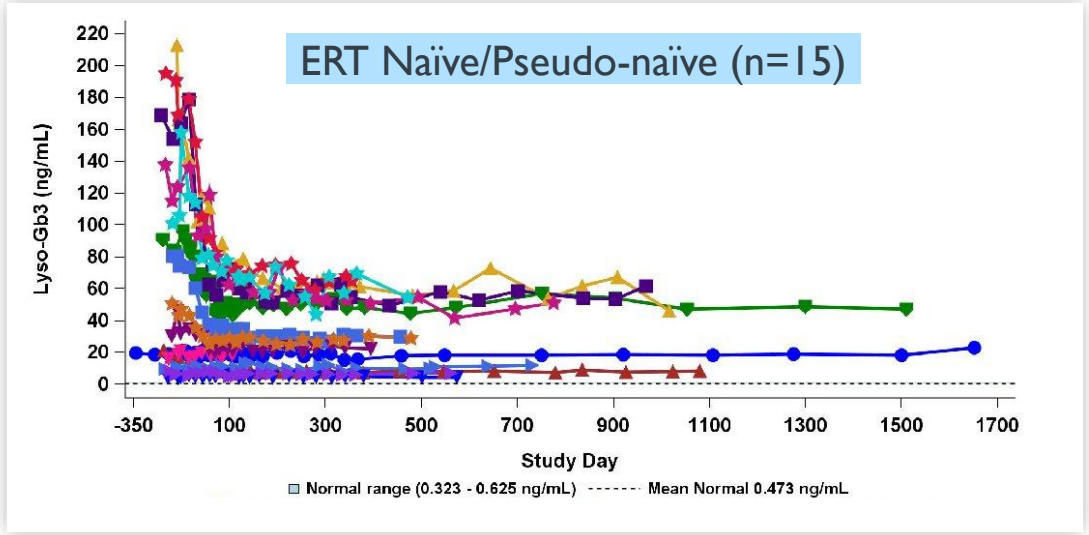
Gal A, alpha galactosidase A; C, cohort; ERT, enzyme replacement therapy

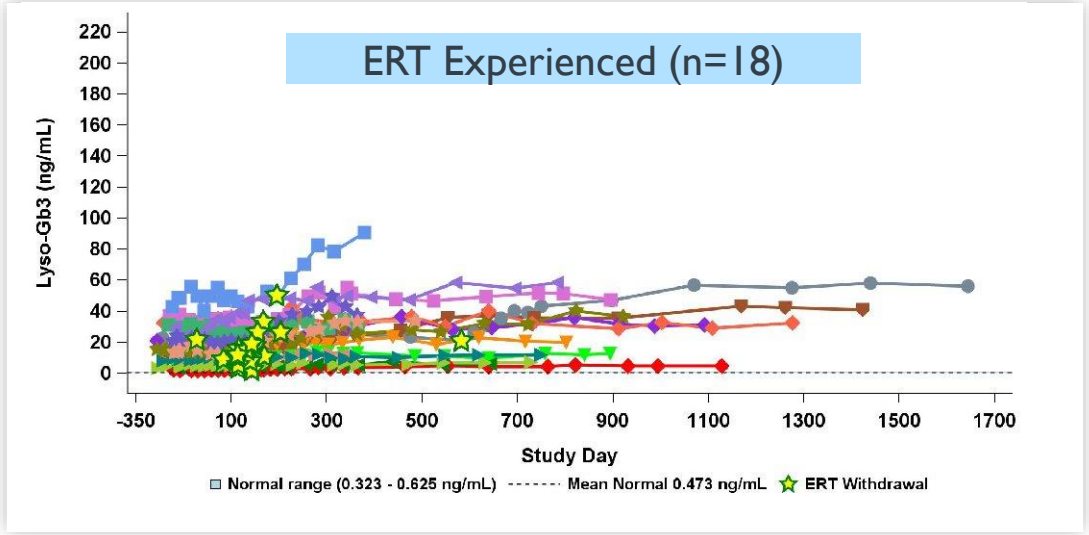
- Fold change relative to mean normal α-Gal A activity (5.32 nmol/h/mL) (n=33):
  - 0.7 to142.9-fold at peak value
  - 0 to 142.9-fold at the last assessment
- Durable supraphysiological activity observed up to 54 months (4.5 years) for the participants (★) with the longest follow-up (n=2)
- 18/18 participants (100%) withdrew from ERT and remained off-ERT as of the data cutoff date of 10 APR 2025
- 17/18 participants (94.4%) maintained supraphysiological levels post-ERT withdrawal

Long-term reduction and stabilization of plasma lyso-Gb3

- For ERT naïve/pseudo-naïve participants
  - Decreases in mean plasma lyso-Gb3 levels were evident from Week 4 to the latest time point tested at Month 48 post-infusion
  - >53% decrease from Week 18 onwards was observed in participants with higher baseline lyso-Gb3 levels (≥60 ng/mL)
- After ERT withdraw, lyso-Gb3 remained stable up to Month 54 (LTS Month 42) post-infusion for most of the participants







Data cut-off date: 10 April 2025
ERT, enzyme replacement therapy; N, number, Lyso-Gb3, globotriaosylsphingosine

Reduction or elimination of antibodies against α-Gal A

	Anti-α-Gal A Total Antibodies Titer		Anti-α-Gal A Neutralizing Antibodies 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: 10 April 2025
α-Gal A, alpha-galactosidase A; TAb, total antibody; NAb, neutralizing antibody; W, week; M, month

- Immunogenicity remains an issue with ERT leading to continuing organ impairment
- 10 participants had measurable titers of TAb or NAb against α-Gal A associated with ERT at baseline
- After ST-920 treatment, TAb or NAb titers decreased markedly in 9 participants and became undetectable in 8 (80%)
- ST-920 treatment did not induce anti-α-Gal A antibodies in seronegative participants

Humoral response to AAV6 capsid had no clinically relevant impact on efficacy or safety outcomes

- All dosed participants (n=33) developed high titers of anti-AAV6 antibodies post ST-920 infusion at all timepoints
- Antibody titers peaked at Week 12 with mean (SD) of 3131458 (3141837) and median (min, max) of 1638400 (409600, 13107200) (n=31)
- Titers gradually declined but remained high through the last timepoint tested at Month 48 post-infusion with mean (SD) of 221867 (179808) and median (min, max) of 204800 (51200, 409600) for 3 participants
- Despite the antibody response, meaningful clinical efficacy and a favorable safety profile were maintained overtime
  - Elevated and durable α-Gal A enzyme activity up to 4.5 years post ST-920 treatment
  - Long-term reduction and stabilization of plasma lyso-Gb3 levels
  - Improved renal function assessed by annualized eGFR slope
  - No safety signals suggest an impact from the development of a humoral response to viral vector capsid

Data cut-off date: 10 April 2025
AAV, adeno-associated virus; α-Gal A, alpha galactosidase A; Lyso-Gb3, globotriaosylsphingosine; eGFR, estimated glomerular filtration rate; SD, standard deviation; N, number

T cell immune responses had no overt impact on α-Gal A activity and safety

- Blood was collected at baseline (n=23) and Week 6 (n=22) post-infusion. PBMCs were analyzed in IFN-γ ELISpot in response to stimulation with AAV6 capsid peptide pools
- AAV6 capsid-specific T-cell response detected
  - 21/23 (91.3%) participants at baseline
  - All available participants (22/22) at Week 6
- Similar response at baseline (13.29 to 423.82 ASV) and Week 6 (4.83 to 445.37 ASV)
- Minimum impact on efficacy and safety
  - Sustained elevations of α-Gal A activity were observed in nearly all participants
  - Only 1/33 participant (3.0%) (subject 24) had mild liver enzyme elevations which were resolved after a limited course of corticosteroid, with no loss of enzyme activity

Heatmap of antigen-specific value (ASV) (spot-forming cells/4E5 PBMCs)

	Baseline			Week 6		
	AAV6 P1	AAV6 P2	AAV6 P3	AAV6 P1	AAV6 P2	AAV6 P3
(Subject 1)	52.13	8.32	5.51	86.76	55.17	20.35
(Subject 3)	300.83	115.07	8.96	391.81	253.79	70.14
(Subject 4)	26.9	-	-	13.39	-	-
(Subject 5)	114.3	24.41	-	30.59	-	-
(Subject 6)	30.96	-	104.9	62.9	43.18	445.37
(Subject 7)	-	-	-	95.67	29.71	14.29
(Subject 8)	41.74	17.79	-	33.99	36.71	17.07
(Subject 9)	38.88	41.43	13.31	44.42	98.46	6.51
(Subject 10)	135.01	11.15	-	81.63	23.56	-
(Subject 12)	8.12	-	-	49.08	10.82	-
(Subject 14)	154.36	-	-	26.54	5.8	6.68
(Subject 16)	13.29	35.36	4.61	15.13	9.07	-
(Subject 17)	81.12	3.08	-	70.45	23.49	21.24
(Subject 18)	423.82	115.22	-	88.59	33.73	22.86
(Subject 20)	58.78	9.56	11.8	352.25	113.23	74.26
(Subject 21)	18.17	-	-			
(Subject 22)	79.69	-	3.37	27.45	-	6.31
(Subject 23)	26.81	-	-	39.61	-	10.78
(Subject 24)	-	-	-	23.46	25.03	23.27
(Subject 25)	86.1	-	-	43.6	-	42.07
(Subject 26)	194.24	10.2	-	67.09	26.41	-
(Subject 28)	55.42	4.29	-	22.69	-	-
(Subject 30)	87.72	-	9.29	79.13	4.83	6.34

Elispot Response: 0-50, 50-100, 100-250, 250-500, >500

Data cut-off date: 10 April 2025

α-Gal A, alpha galactosidase A; ASV, antigen-specific value; INF-γ, interferon gamma; PBMC, peripheral blood mononuclear cell; N, number

Summary

- ST-920 vector DNA shedding peaked within 2 weeks and **fully cleared** from urine, saliva, stool, semen and plasma ranging from 3.1 to 87.4 days
- **Durable transgene expression** was demonstrated with supraphysiological α-Gal A activity up to **4.5 years**
- **Sustained pharmacodynamic response of** long-term reduction and stabilization of plasma lyso-Gb3 levels
- Total or neutralizing α-Gal A antibodies **decreased** markedly in 9 of 10 subjects and became **undetectable** in 8 (80%)
- Antibody response to AAV6 capsid **had no clinically relevant impact on efficacy or safety outcomes**
- T cell immune responses assessed by IFN-γ ELISpot **had no overt impact** on α-Gal A activity and safety. Only 1 participant had mild increases in liver enzymes
- **One time treatment of ST-920 (isaralgagene civaparvovec) demonstrated durable transgene expression, sustained pharmacodynamic response and favorable immunogenicity profile for Fabry disease in adults**
- Our team intends to complete submission of a **BLA for ST-920 in 2026 under the Accelerated Approval pathway**

Data cut-off date: 10 April 2025

Acknowledgements

Investigators:

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