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

Poster #232

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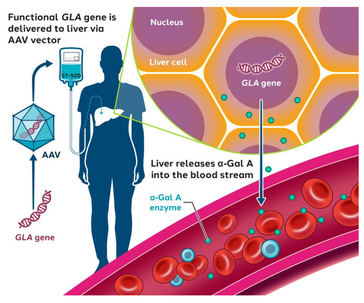
Introduction

- Fabry disease is a progressive, multi-organ, lysosomal storage disease caused by pathogenic mutations in the *GLA* gene leading to deficiency of the lysosomal enzyme alpha-galactosidase A (α-Gal A) and accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3)
- Isaralgagene civaparvovec (ST-920) is an investigational gene therapy using a recombinant adeno-associated virus (AAV)2/6 vector containing human *GLA* cDNA designed to produce continuous, liver-specific α-Gal-A expression
- A gene therapy approach offers potential advantages:
  - Convenient one-time administration
  - Potential to eliminate repeated enzyme replacement therapy (ERT) infusions
  - Durable efficacy
  - Low immunogenicity to transgene product
  - No prophylaxis with steroids or other immunomodulating agents



- This Phase 1/2 open-label, multicenter study (STAAR aka ST-920-201) evaluate ST-920 in adults with symptomatic Fabry Disease (NCT04046224)

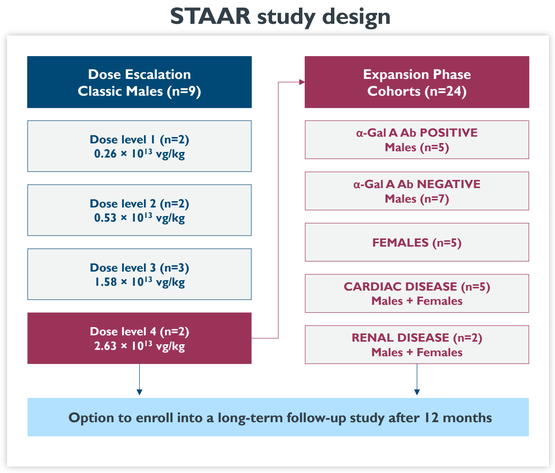
Study overview

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

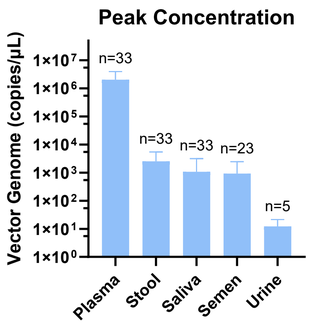
Main objectives
- Safety and tolerability of ST-920
- Vector DNA shedding
- α-Gal A activity and change in plasma lyso-Gb3
- Impact on ERT administration
- Renal and cardiac function
- Patient-reported outcomes and quality of life scores
- Immunogenicity

Study data
- The completed Phase 1/2 study (n=33)
- Long-term follow-up of participants 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

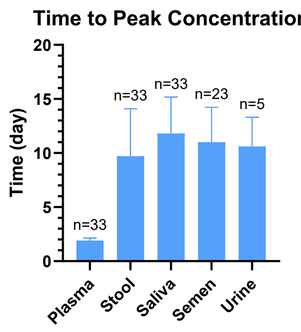
STAAR study design



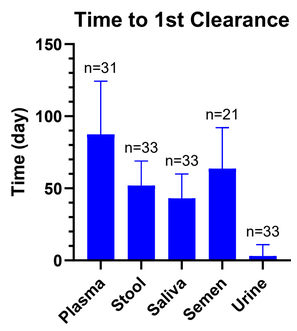
ST-920 vector DNA fully cleared from shedding matrices



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



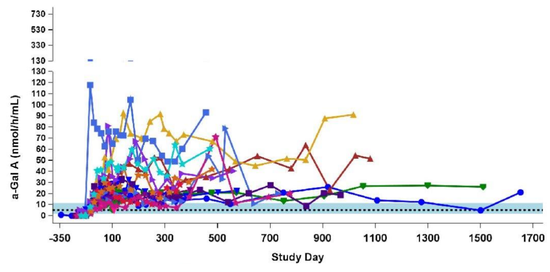
- Time to peak concentration ranged from 1.9 (plasma) to 11.8 (saliva) days



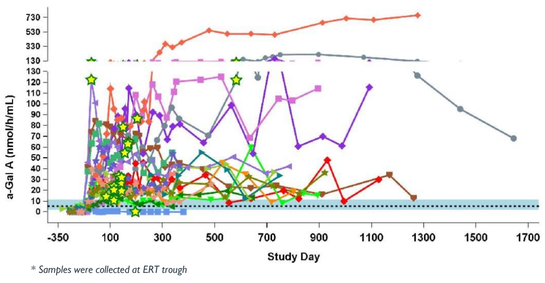
- Clearance time (day) (low to high): Urine (3.1), saliva, stool, semen and plasma (87.4)

Sustained supraphysiological plasma α-Gal A activity

ERT Naïve/Pseudo-naïve (n=15)

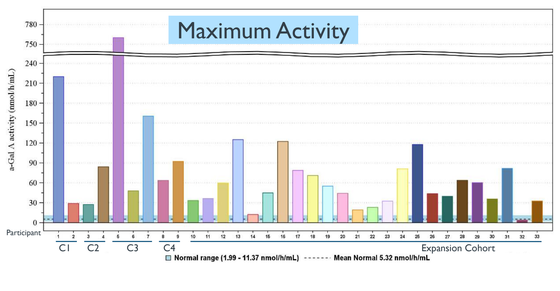


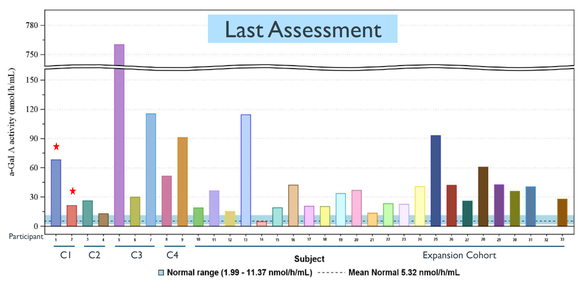
ERT Experienced (n=18)*



* *Samples were collected at ERT trough*

- 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 was observed in ERT naïve/pseudo-naïve participants

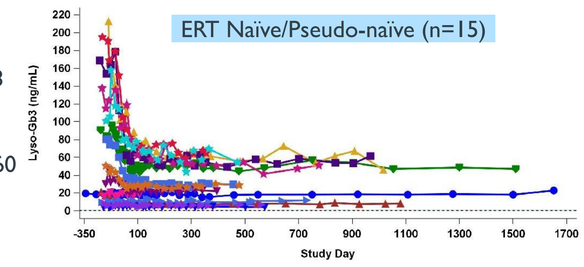


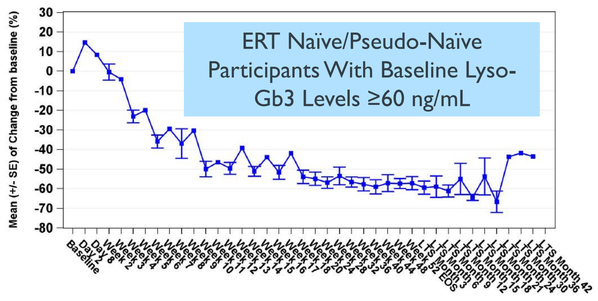


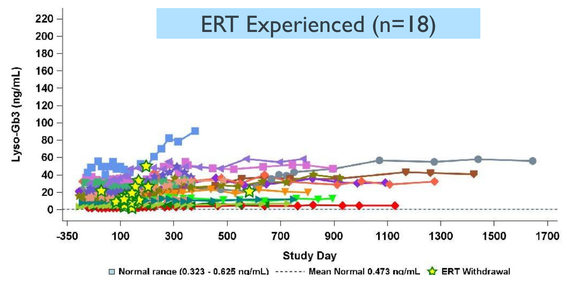
- Fold change relative to mean normal α-Gal A activity (5.32 nmol/h/mL) (n=33):
  - 0.7 to142.9-fold at peak value
  - 0 to 142.9-fold at the last assessment
- Durable supraphysiological activity observed up to 54 months (4.5 years) for the participants (⋆) with the longest follow-up (n=2)
- 18/18 participants (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 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







Reduction/elimination of antibodies against α-Gal A

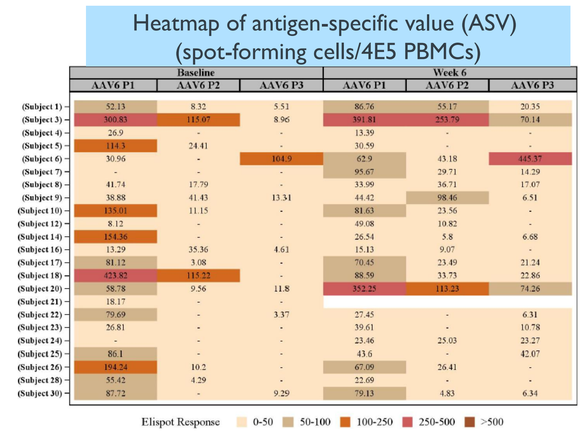
	Anti-α-Gal A Total Antibodies (TAb) Titer		Anti-α-Gal A Neutralizing Antibodies (NAb) Titer	
	Baseline	On-study	Baseline	On-study
Participant 1	1280	Undetectable (M24)	160	Undetectable (W36)
Participant 3	160	Undetectable (W24)	Undetectable	Undetectable
Participant 4	160	Undetectable (W52)	Undetectable	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)

- Immunogenicity remains an issue with ERT leading to continuing organ impairment
- 10 participants had measurable titers of total antibodies (TAb) or neutralizing antibodies (NAb) against α-Gal A associated with ERT at baseline
- After ST-920 treatment, TAb or NAb titers decreased markedly in 9 (90%) participants and became undetectable in 8 (80%)
- ST-920 treatment did not induce anti-α-Gal A antibodies in seronegative participants

Humoral and cellular response to AAV6 capsid

- 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 (standard deviation [SD]) of 3131458 (3141837) and median (min, max) of 1638400 (409600, 13107200) (n=31)
  - No clinically relevant impact on efficacy or safety
- AAV6 capsid-specific T-cell response by ELISpot
  - Detected in 21/23 (91.3%) participants at baseline and all available participants (22/22) at Week 6
  - Minimum impact on efficacy and safety. Only 1/33 participant (3.0%) (participant 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)



Summary and conclusions

- 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 participants and became **undetectable** in 8 participants (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**

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