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Isaralgagene Civaparvovec (ST-920) Shows Positive Mean Annualized eGFR Slope in Adults with Fabry Disease: Updated Results from the Registrational Phase 1/2 STAAR Gene Therapy Study

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Summary

- Totality of data supports the potential for isaralgagene civaparvovec as a one-time, durable treatment of the underlying pathology of Fabry disease to provide meaningful, multi-organ, clinical benefits above current standards of care.
- STAAR study demonstrated positive mean annualized estimated glomerular filtration rate (eGFR) slope at 52-weeks across all dosed subjects in the study and at 104-weeks for 19 subjects.
- Stable cardiac function was observed over at least one year.
- Key secondary endpoints in the study were also positive and patients demonstrated a range of other clinical benefits, including improvements in quality of life (QoL) data.
- Isaralgagene civaparvovec demonstrated a favorable safety and tolerability profile, without the need for preconditioning.
- Sangamo intends to submit a Biologics License Application (BLA) under the Accelerated Approval pathway in 2026.

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 AAV2/6 vector containing human *GLA* cDNA designed to produce continuous, liver-specific α-Gal-A expression.
- This Phase 1/2 open-label, multicenter study (STAAR) evaluated ST-920 in adults with symptomatic Fabry Disease (NCT04046224) with long-term follow-up (NCT05039866).

Study design

Key eligibility criteria

- Age ≥18 with symptomatic Fabry disease
  - Enzyme Replacement Therapy (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

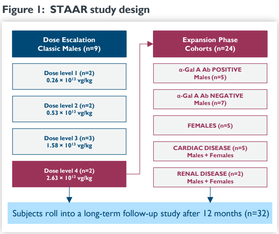
Primary objective

- Safety and tolerability of ST-920

Other objectives

- 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

Figure 1: STAAR study design



Statistical methods

- Two methods were employed to estimate the mean eGFR slope and its 95% confidence interval (CI). First, individual eGFR slopes at Week 52/104 were estimated using a linear regression model in a two-step process. Separately, a mixed model with random intercept and random slope (RIRS) was used for estimation.

Study schema (Figure 1)

- Four dose levels were evaluated in the dose escalation phase (n=9); the recommended dose for further evaluation was 2.63 x 10^{13} vector genomes per kilogram (vg/kg) (measured by digital droplet PCR; same as 5 x 10^{13} vg/kg by quantitative PCR).
- 24 subjects were subsequently enrolled into 5 expansion phase cohorts.
- All subjects were offered the option to enroll into a long-term follow-up study after 12 months.
- At the discretion of the Investigator, subjects receiving ERT were withdrawn from ERT ≥4 weeks following ST-920 administration.

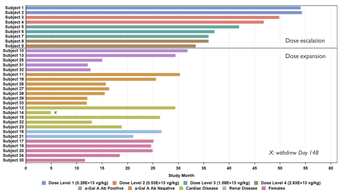
Results

Table 1: Baseline characteristics: Dose escalation and dose expansion phases

	Dose escalation (n=9)	Dose expansion (n=24)	All (n=33)
Age, median (range)	42 (22-50)	41.5 (18-67)	42 (18-67)
Sex (M:F)	9:0	14:10	23:10
ERT status (n):			
• Naïve	2	7	9
• Pseudo-naïve	2	4	6
• On ERT	5	13	18
Baseline Fabry symptoms (n):			
• Cornea verticillata	4	10	14
• Paresthesia	3	7	10
• Anhidrosis	1	5	6
• Angiokeratoma	2	9	11
eGFR$_{CKD-EPI}$ category, (n):			
• >90 ml/min/1.73 m^2	4	13	17
• 60-90 ml/min/1.73 m^2	4	8	12
• 40-<60 ml/min/1.73 m^2	1	3	4

- Data on 33 subjects (data cutoff date: 10 Apr 2025) are reported in this analysis.
- Enrollment, dosing and 1 year follow-up are complete.
- The baseline characteristics of all subjects are shown in Table 1.

Figure 2: Follow-up in months: Dose escalation and dose expansion phases



- Median duration of follow-up: 24 months (21.1 weeks – 54.3 months)
- 32 subjects have ≥ 12 months of follow-up
- 19 subjects have ≥ 24 months of follow-up
- Subject 14 withdrew from the study at Day 148 post-dosing, due to patient decision

Efficacy

Figure 3: Positive mean eGFR slopes were observed at weeks 52 and 104

A positive mean annualized eGFR slope, indicating an improvement in renal function, was observed at week 52 in 32 subjects who had completed 52-weeks follow-up, and week 104 for 19 subjects who had completed 104-weeks follow-up. This compares favorably to those receiving approved Fabry treatments.

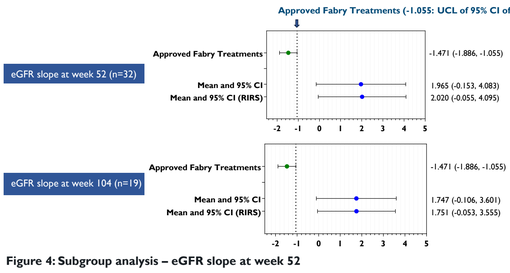
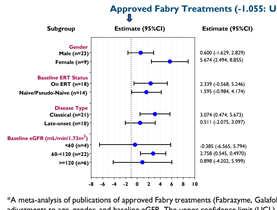


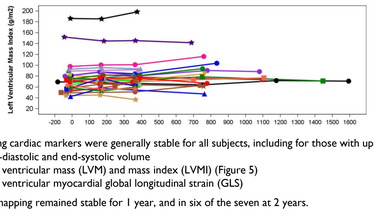
Figure 4: Subgroup analysis – eGFR slope at week 52



- Supportive mean annualized eGFR slopes were observed across subgroups, including gender, baseline ERT status, Fabry disease type and baseline eGFR, demonstrating consistency in effect across Fabry patients.

*A meta-analysis of publications of approved Fabry treatments (Fabrazyme, Galafold, Replagal) was conducted. The mean and 95% CI were calculated with adjustments to age, gender, and baseline eGFR. The upper confidence limit (UCL) of the 95% CI, -1.055 mL/min/1.73m2/year, was used to rule out variability in data and serves as a conservative historical comparator for Fabry patients treated with approved therapies.

Figure 5: Cardiac endpoints showed stability over an extended period (n=33)



- The following cardiac markers were generally stable for all subjects, including for those with up to 4 years' data:
  - End-diastolic and end-systolic volume
  - Left ventricular mass (LVM) and mass index (LVMI) (Figure 5)
  - Left ventricular myocardial global longitudinal strain (GLS)
- T1 and T2 mapping remained stable for 1 year, and in six of the seven at 2 years.
- MRI: Left ventricular Ejection Fraction (percent) stability over 1 year in all subjects and trend of increase in 50% of patients who have reached week 104 timepoint.
- Troponin (ng/L) and Pro-B-type Natriuretic Peptide (pg/ml) levels stable for all subjects except one

References:

1. Stewart AL, Greenfield S, Hays RD, Wells K, Rogers WH, Berry SD, et al. Functional status and well-being of patients with chronic conditions. Results from the medical outcomes study. JAMA. 1989;262:907–13

Figure 6: Normal to supraphysiological levels of plasma α-Gal A and reductions in lyso-Gb3 in naïve/pseudo-naive subjects (n=15)

Fig 6a: Plasma α-Gal A activity

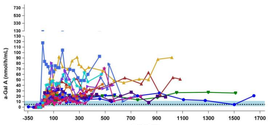
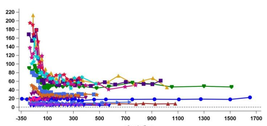


Fig 6b: Plasma lyso-Gb3 levels



- Sustained normal to supraphysiological α-Gal A activity was maintained up to 54 months for all naïve/pseudo-naïve subjects (Fig. 6a).
- Largest reductions in plasma lyso-Gb3 seen in subjects with highest levels at baseline. Long-term stabilization of lyso-Gb3 levels was observed (Fig. 6b).

Figure 7: Sustained elevated levels of plasma α-Gal A and stable levels of lyso-Gb3 following ERT withdrawal in ERT-treated subjects (n=18)

Fig 7a: Plasma α-Gal A activity

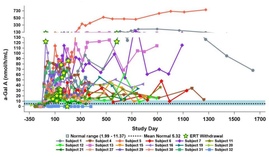
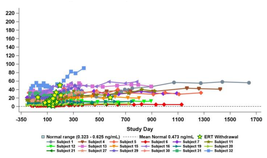


Fig 7b: Plasma lyso-Gb3 levels



- Sustained elevated levels of α-Gal A activity were observed for 17 of the 18 ERT-treated subjects (Fig 7a). Subject 32 exhibited below normal levels of α-Gal A activity as of the data cutoff date.
- Plasma lyso-Gb3 levels remained stable following ERT withdrawal for up to **33 months** for all ERT subjects (Fig 7b)
- Following dosing with ST-920, all 18 subjects who came into the study on ERT were able to safely withdraw from ERT – with one subject off ERT for more than three years.
- Since the data cutoff date, a physician has decided to resume ERT for one of their treated subjects who had withdrawn from ERT. This subject, who received ST-920 more than two and a half years ago, maintained supraphysiological levels of a-Gal A activity, and their lyso-Gb3 levels were generally stable as of the data cutoff date.

Significant improvement seen in disease severity, QoL and gastrointestinal (GI) symptoms

Table 2: FOS-MSSI scores in subjects with ≥12 m follow-up (n=32)

Subject	ERT status at Baseline	FOS-MSSI category Baseline	FOS-MSSI category Week 52	FOS-MSSI category Week 104	FOS-MSSI category Year 3	FOS-MSSI category Year 4
1	ERT	Moderate	Moderate		Moderate	Mild
2	Pseudo-naive	Mild	Mild	Mild	Mild	Mild
3	Pseudo-naive	Moderate	Mild	Mild	Mild	Mild
4	ERT	Mild	Mild	Mild	Mild	Mild
5	ERT	Moderate	Mild	Moderate	Moderate	
6	ERT	Moderate	Mild	Mild	Moderate	
7	ERT	Severe	Moderate	Moderate	Moderate	
8	Naive	Moderate	Mild	Mild	Mild	
9	Naive	Moderate		Moderate		
10	Pseudo-naive	Moderate	Moderate	Moderate		
11	ERT	Moderate	Moderate	Moderate		
12	ERT	Mild	Mild	Mild		
13	ERT	Mild	Mild	Mild		
14	ERT	Mild	Mild	Mild		
15	ERT	Mild	Mild	Mild		
16	ERT	Moderate	Moderate	Moderate		
17	Naive	Moderate	Mild	Mild		
18	Naive	Moderate	Moderate	Moderate		
19	ERT	Mild	Moderate	Mild		
20	ERT	Moderate	Moderate	Mild		
21	ERT	Moderate	Mild			
22	Naïve	Mild	Mild			
23	Naive	Mild	Mild			
24	Pseudo-naive	Moderate	Moderate			
25	Pseudo-naive	Mild	Mild			
26	Naïve	Moderate	Mild			
27	ERT	Mild	Mild			
28	Naïve	Mild	Mild			
29	ERT	Moderate	Mild			
30	ERT	Mild	Mild			
31	ERT	Mild	Mild			
32	ERT	Moderate	Moderate			
33	Naive	Mild	Mild			

FOS-MSSI (Fabry Outcome Survey adaptation of the Mainz Severity Score Index)

- At 12 months, 22 (69%) subjects improved their total MSSI score and 9 improved their MSSI categories from baseline compared to last assessment.
- 14 were mild at baseline and at last assessment.
- Age-adjusted MSSI score mean change from baseline at Week 52 and 95% CI was -4.21 [-6.2, -2.2], p=0.0002.

SF-36 (Short form-36):

- Significant improvements in the SF-36 quality of life scores, including role-physical +14.8 (95% CI: 7.3, 22.4, p=0.0003), vitality +9.6 (95% CI: 3.9, 15.2, p=0.0017), bodily pain +9.0 (95% CI: 2.3, 15.7, p=0.0104), social functioning +7.8 (95% CI: 2.0, 13.6, p=0.0100), general health +7.4 (95% CI: 2.0, 12.8, p=0.0091), and physical component scores +4.2 (95% CI: 1.8, 6.6, p=0.0014), were observed at week 52 compared to baseline.

GSRS (GI Symptom Rating Scale):

- Mean change from baseline at Week 52 in GSRS (-0.24 [-0.4, -0.1], p=0.0087), diarrhea (-0.50, [-0.8, -0.2], p=0.0048).
- All p-values are unadjusted nominal p-values.

Reduction or elimination of antibodies against α-Gal A

Table 3: Anti-α-Gal A total and neutralizing antibody titers

	Anti-α-Gal A Total Antibodies (TAb) Titer		Anti-α-Gal A Neutralizing Antibodies (NAb) Titer	
	Baseline	On-study	Baseline	On-study
Subject 1	1280	Undetectable (M24)	160	Undetectable (W36)
Subject 3	160	Undetectable (W24)	Undetectable	Undetectable
Subject 4	160	Undetectable (W52)	Undetectable	Undetectable
Subject 5	10240	Undetectable (M36)	320	Undetectable (M36)
Subject 10	80	Undetectable (W4)	10	Undetectable (W4)
Subject 13	5120	40 (M24)	160	10 (M24)
Subject 16	2560	Undetectable (M24)	40	Undetectable (W52)
Subject 25	160	Undetectable (W4)	160	Undetectable (W4)
Subject 31	80	Undetectable (W12)	10	Undetectable (W4)
Subject 32	20480	10240 (W52)	640	640 (W52)

- Progressive organ impairment linked to immunogenicity remains an issue with ERT.
- 10 subjects 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 and/or NAb titers decreased markedly in 9 (90%) subjects and became undetectable in 8 (80%) subjects.**
- ST-920 treatment did not induce anti-α-Gal A antibodies in seronegative subjects.

Safety

Table 4: Summary of treatment-emergent adverse events in ≥10% of subjects

AE by preferred term	Treated subjects (n=33)	
	All grades	Grade 3-4
Pyrexia	20 (60.6%)	1 (3.0%) (G3)
COVID-19	12 (36.4%)	0
Nasopharyngitis	11 (33.3%)	0
Headache	10 (30.3%)	0
Fatigue	9 (27.3%)	0
Nausea	9 (27.3%)	0
Diarrhea	6 (18.2%)	0
Paresthesia	5 (15.2%)	0
Myalgia	5 (15.2%)	1 (3.0%) (G3)
Dizziness	5 (15.2%)	0
Cough	5 (15.2%)	0
Abdominal Pain	4 (12.1%)	0
Palpitations	4 (12.1%)	0
Hypotension	4 (12.1%)	0
Infusion Related Reaction	4 (12.1%)	0
Urinary Tract Infection	4 (12.1%)	0
Dyspnoea	4 (12.1%)	0

- ST-920 demonstrated a favorable safety and tolerability profile in the study, without the requirement for preconditioning.
- The majority of adverse events (AE) were Grade 1-2, as of the 10 April 2025 cut-off date.
- Seven treatment emergent serious adverse events (TESAEs) were reported in five subjects, all Grade 2 or Grade 3:
  - Left arm pain, non-cardiac chest pain, sepsis, shoulder enthesopathy, pain in extremity, cerebrovascular accident, brain stem stroke
- All TEAEs resolved in response to clinical management.
- There were no safety-related study discontinuations, and no deaths.

Conclusions

- **Totality of data supports the potential for ST-920 as a one-time, durable treatment of the underlying pathology of Fabry disease to provide meaningful, multi-organ, clinical benefits above current standards of care.**
- **A positive mean annualized eGFR slope was** observed in 32 subjects with 52-weeks of follow-up and 19 subjects with 104-weeks follow-up, indicating improvements in renal function. This compares favorably to published data in Fabry patients who received approved therapies.
- **Stable cardiac function** was observed over one and two years.
- **Durable efficacy** was demonstrated with elevated expression of α-Gal A activity observed up to 4.5 years for the longest treated subject.
- All 18 patients who began the study on ERT had been **withdrawn from ERT** and remained off ERT as of the cutoff date.
- **Clinically and statistically significant QOL improvements were observed:**
  - 69% of subjects saw an improvement in FOS-MSSI score.
  - Significant improvements in the SF-36 quality of life scores observed.
  - Improvements in gastrointestinal symptoms.
- **Total and/or neutralizing α-Gal A antibodies decreased** markedly in 9 (90%) subjects and were undetectable in 8 (80%) out of 10 antibody positive subjects.
- ST-920 demonstrated a **favorable safety and tolerability profile** in the study, without the requirement for preconditioning
- **ST-920 has potential as a one-time, durable treatment option for Fabry disease that can improve patient outcomes.**
- Sangamo intends to submit a BLA for ST-920 in 2026 under the Accelerated Approval pathway.

Acknowledgments

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