# Preliminary results of STAAR, a Phase 1/2 study of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease and long-term follow-up

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# Disclosures information (Patrick Deegan, MD)

I have the following financial relationships to disclose:

- **Consulting Fees/Advisory Boards**: Sanofi Genzyme, Protalix Biotherapeutics, Amicus Therapeutics
- **Contracted Research**: (Clinical Trial PI) Sangamo Therapeutics, Sanofi Genzyme, Protalix Biotherapeutics, Amicus Therapeutics

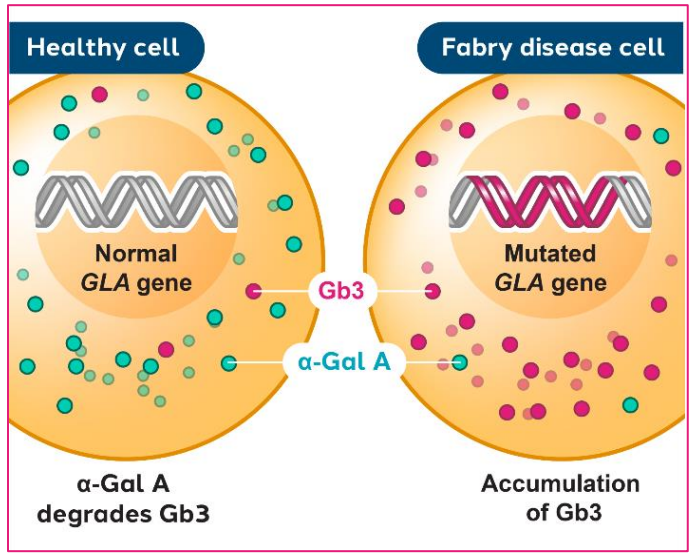
I will discuss the following investigational use in my presentation:

- Use of isaralgagene civaparvovec (ST-920) gene therapy in adults with Fabry disease

Funding for this study was provided by Sangamo Therapeutics

# Fabry Disease Overview

## Mechanism of disease and biomarkers




**Clinical biomarkers:**
α-Gal A activity, Gb3, lyso-Gb3

## Organs and systems impacted

**Kidney**
Progressive kidney disease

**Cardiovascular**
Heart failure, strokes/TIA

**Skin**
Rashes, temperature sensitivity, abnormal sweating

**Neuropathic pain**
Burning/tingling commonly in extremities

**Other**
GI disturbances, hearing loss, vision problems, mood disorders

## Reduced patient quality of life

### Physical health impacts

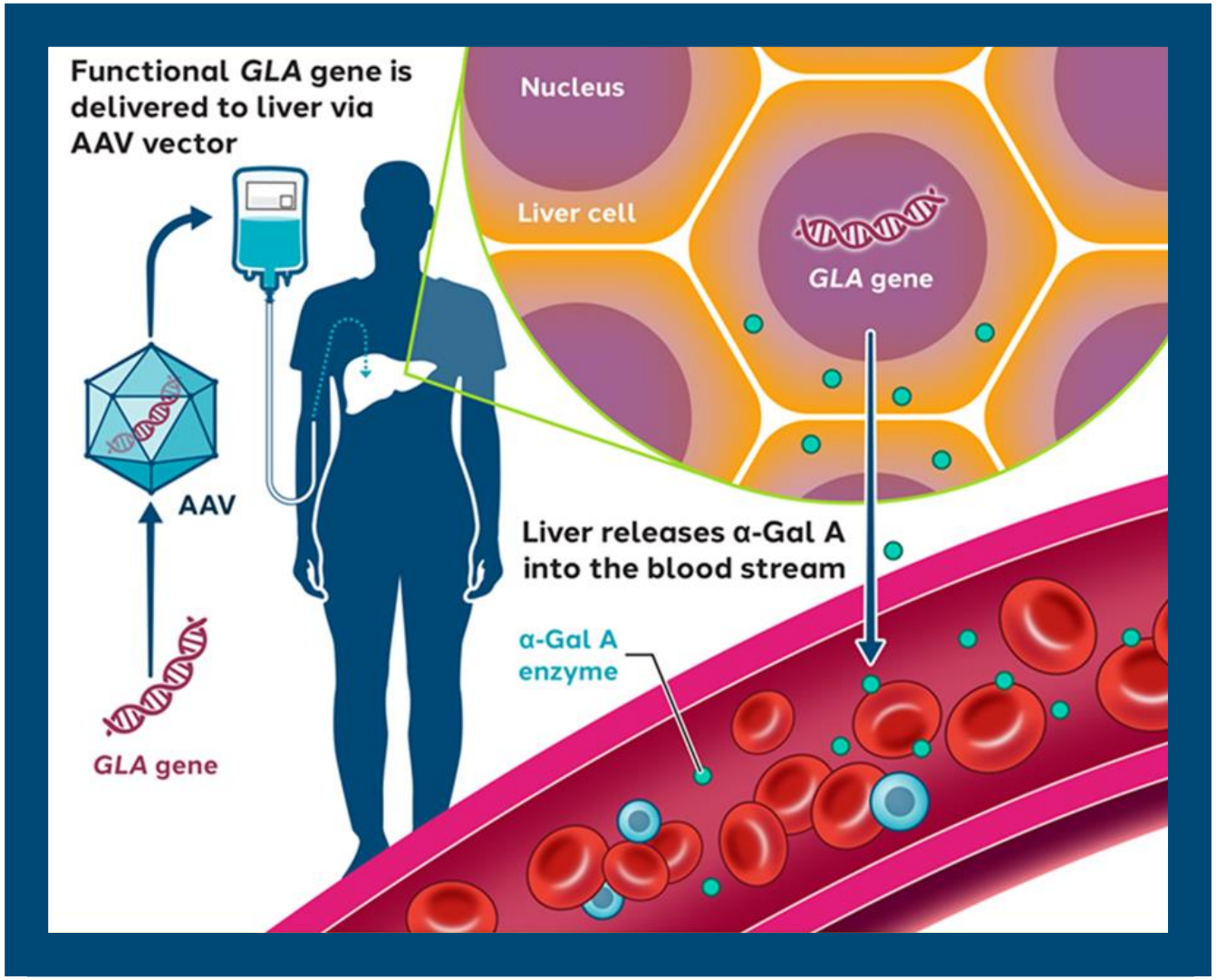
- Chronic pain
- Shortened lifespan
- Inability/difficulty performing normal daily activities
- Temperature intolerance due to inability to sweat

### Mental health impacts

- Depression and anxiety
- Change in sleep patterns
- Social functioning

α-Gal A, alpha-galactosidase A; Gb3, globotriaosylceramide; GI, gastrointestinal; GLA, galactosidase alpha; lyso-Gb3, globotriaosylsphingosine; TIA, transient ischemic attack.

# Isaralgagene civaparvovec (ST-920): one-time, liver-directed gene therapy candidate for the treatment of Fabry disease




## Goals of Treatment

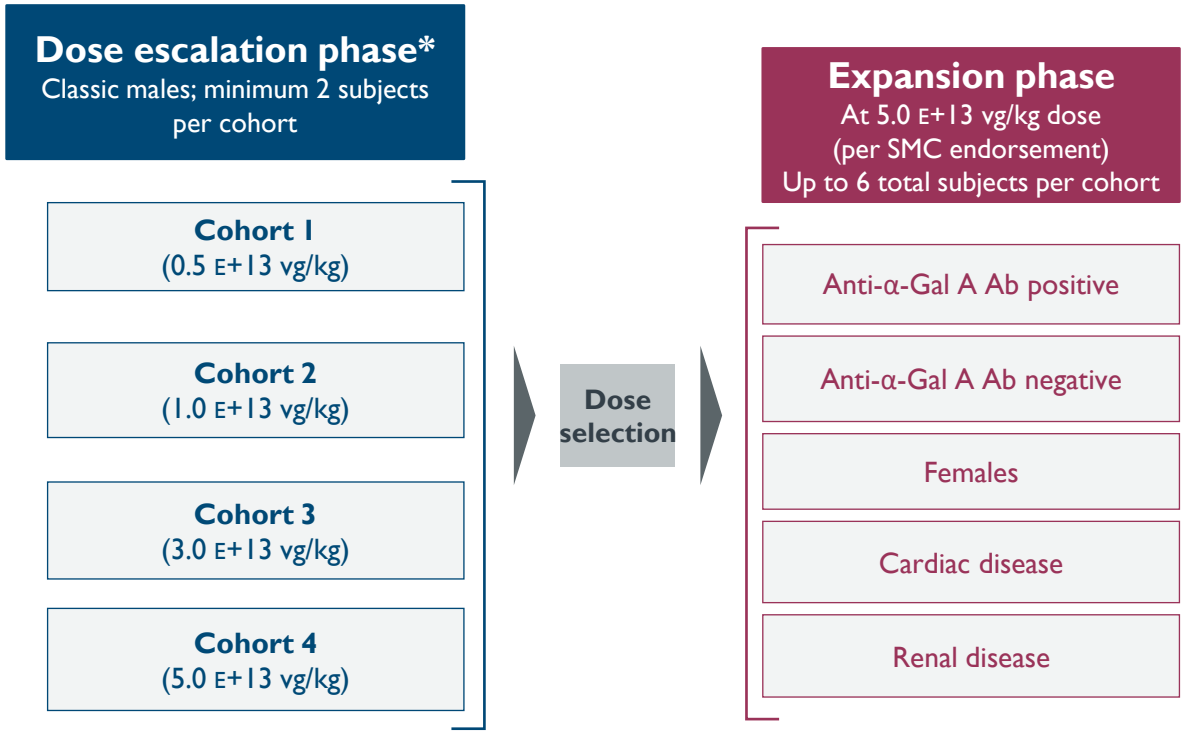
- Administer a one-time infusion without the need for prophylactic steroid treatment
- Deliver long-lasting improvement of symptoms most important to patients
- Eliminate the need for frequent ERT infusions

α-Gal A, alpha galactosidase A; 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




## 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)

*Safety and efficacy data of each cohort was reviewed by a safety monitoring committee (SMC) prior to dose escalation.

α-Gal A, alpha galactosidase A; AAV, adeno-associated virus; Ab, antibody; ERT, enzyme replacement therapy; QoL, quality of life; vg/kg, vector genomes per kilogram of body weight.

# STAAR & LTFU: Dose Escalation Baseline Subject Characteristics

| | Cohort 1 (n=2) 0.5e13 vg/kg | | Cohort 2 (n=2) 1.0e13 vg/kg | | Cohort 3 (n=3) 3.0e13 vg/kg | | | Cohort 4 (n=2) 5.0e13 vg/kg | |
|---|---|---|---|---|---|---|---|---|---|
| | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 | Subject 6 | Subject 7 | Subject 8 | Subject 9 |
| Age (years) | 48 | 25 | 42 | 22 | 39 | 42 | 51 | 49 | 40 |
| ERT | Agalsidase beta | Pseudo-naïve to ERT | Pseudo-naïve to ERT | Agalsidase beta | Agalsidase beta | Agalsidase beta | Agalsidase beta | No (Naïve) | No (Naïve) |
| Plasma α-Gal A activity (nmol/h/mL)* | 1.54 | Below LOQ | Below LOQ | 2.24 | 0.91 | Below LOQ | Below LOQ | 0.96 | Below LOQ |
| Plasma lyso-Gb3 (ng/mL)* | 22.1 | 18.1 | 83.2 | 11.1 | 32.9 | 1.91 | 16.3 | 16.9 | 167 |
| Primary disease signs and symptoms | Hypohidrosis<br>Tinnitus and vertigo<br>Left ventricular hypertrophy<br>Palpitations<br>Anemia<br>Leg edema | Anhidrosis<br>Tinnitus<br>Acroparesthesia†<br>Sinus bradycardia<br>Left ventricular hypertrophy | Hypohidrosis<br>Tinnitus and vertigo<br>Acroparesthesia†<br>ECG sinus arrhythmia | Hypohidrosis<br>Neuropathic pain<br>Aortic root dilation | Tinnitus<br>High-frequency hearing loss<br>Acroparesthesia†<br>Sinus bradycardia<br>Loose stool and constipation | Hypohidrosis<br>Tinnitus<br>Neuropathic pain<br>Acroparesthesia† | Depression<br>Ventricular tachycardia<br>Hearing loss<br>Neuropathic pain | Tinnitus<br>Mild ventricular hypertrophy<br>Acroparesthesia† | Mild ventricular wall thickness |
| Renal function (eGFR; mL/min/1.73 $m^2$)*‡ | 101.4 | 111.4 | 112.9 | 100 | 91.5 | 80 | 63.8 | 45.4 | 82.1 |
| Pre-existing α-Gal A Abs | Positive | Negative | Positive | Positive | Positive | Negative | Negative | Negative | Negative |
| Mutation | G261D | T141I | W340R | S297Y | Q283X | N215S | c.801+3A>G | P362L | T141I |
| Length of follow-up | 23 months | 22.2 months | 17.6 months | 14.1 months | 40.3 weeks | 26.3 weeks | 16.4 weeks | 16.4 weeks | 14.1 weeks |

*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.

# No treatment-related serious adverse events reported

| 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=3) | | Cohort 4 (5.0e13 vg/kg) (n=2) | | Overall (N=9) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Events | n | Events | n | Events | n | Events | n | Events |
| **Treatment-related adverse events (total)** | **1** | **3** | **1** | **2** | **1** | **6** | **2** | **6** | **5** | **17** |
| Pyrexia | - | - | 1 | 2 | 1 | 1 | 1 | 1* | 3 | 4 |
| Headache | - | - | - | - | 1 | 1 | 1 | 1 | 2 | 2 |
| Chills | - | - | - | - | - | - | 1 | 1 | 1 | 1 |
| Hemoglobin decreased | 1 | 1 | - | - | - | - | - | - | 1 | 1 |
| Platelet count increased | 1 | 1 | - | - | - | - | - | - | 1 | 1 |
| Rash | 1 | 1 | - | - | - | - | - | - | 1 | 1 |
| Myalgia | - | - | - | - | - | 1 | - | - | 1 | 1 |
| Arthralgia | - | - | - | - | - | - | 1 | 1 | 1 | 1 |
| Fatigue | - | - | - | - | 1 | 1 | - | - | 1 | 1 |
| Abdominal pain | - | - | - | - | 1 | 1 | - | - | 1 | 1 |
| Frequent bowel movements | - | - | - | - | 1 | 1 | - | - | 1 | 1 |
| Diarrhea | - | - | - | - | - | - | 1 | 1 | 1 | 1 |
| Weight increased | - | - | - | - | - | - | 1 | 1 | 1 | 1 |

As of the cutoff date of July 21, 2022, length of follow-up ranged from 14.1 weeks to 23 months.

*Grade 2 pyrexia in Subject 8

MedDRA, Medical Dictionary for Regulatory Activities; LTFU, long-term follow-up; vg/kg, vector genomes per kilogram of body weight.

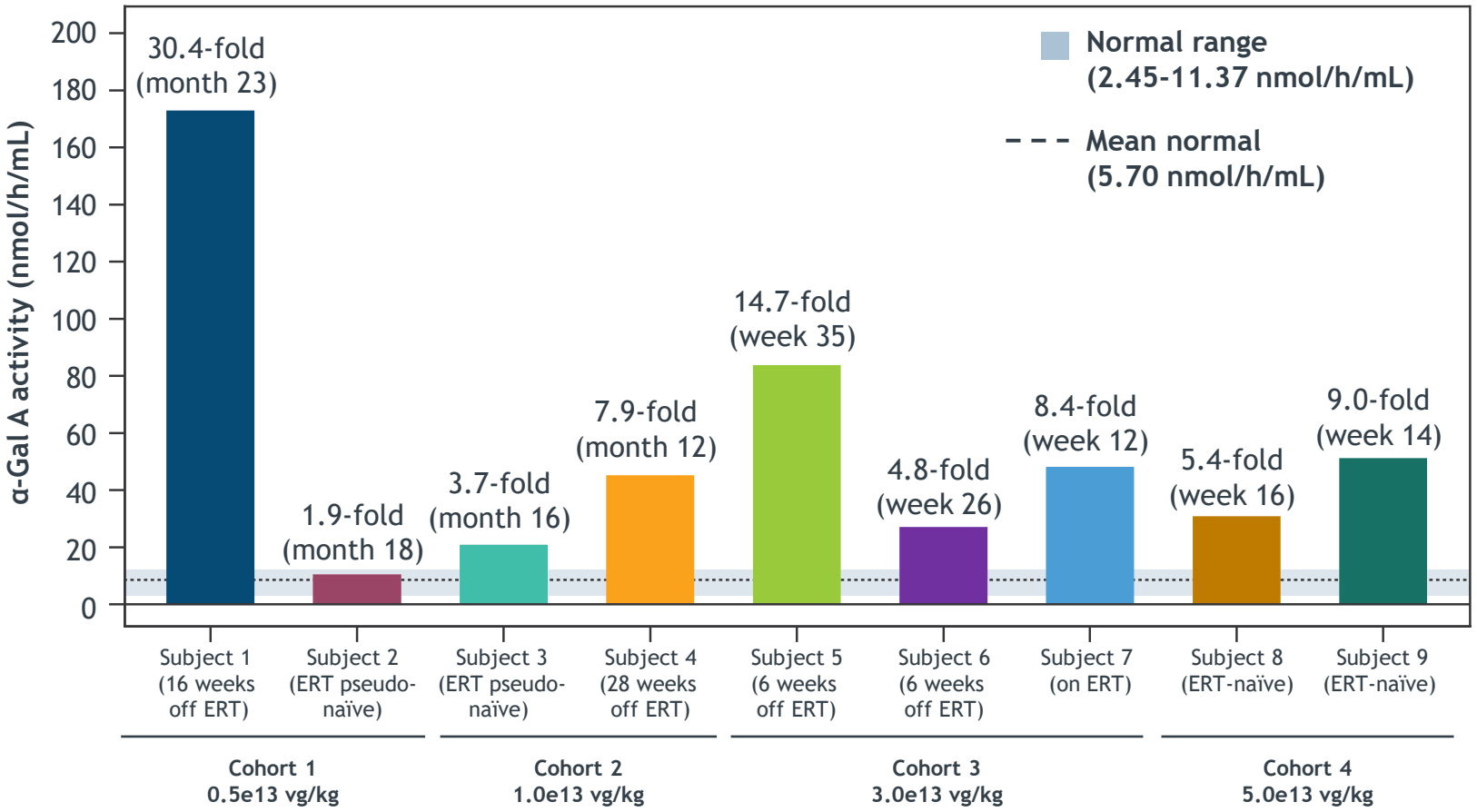
Isaralgagene civaparvovec (ST-920) continued to be generally well tolerated

No subjects have been treated with steroids, either prophylactically or reactively

No treatment-related serious adverse events were reported

All treatment-related adverse events were Grade 1 (mild) with the exception of one pyrexia Grade 2 (moderate)

# Elevated plasma α-Gal A activity reported across all nine subjects in dose escalation, including LTFU



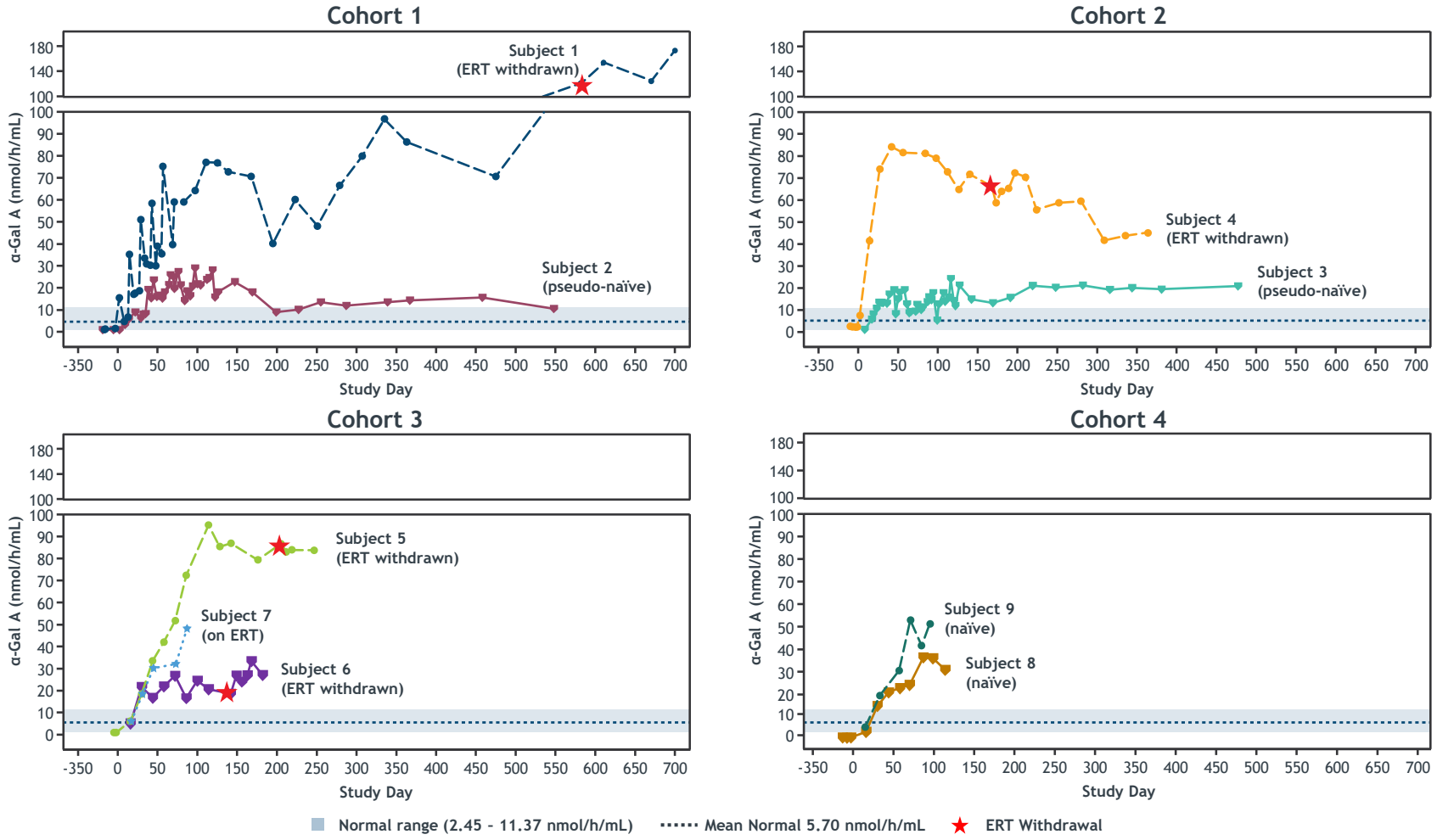

Data presented as of the cutoff date of July 21, 2022. Fold change was calculated at last measured time point. α-Gal A activity was measured using a 3-hour reaction time and is presented in nmol/h/mL. For Subject 7, sampling was at ERT trough. Normal range and mean normal were determined based on healthy male individuals. α-Gal A, alpha galactosidase A; ERT, enzyme replacement therapy; LTFU, long-term follow-up

Elevated α-Gal A activity was sustained through the last sampling point for 9 subjects across all 4 dose cohorts as of July 21, 2022, data cutoff

All four subjects (1-4) in LTFU maintained elevated α-Gal A levels for 1 year or more

Four subjects underwent ERT withdrawal and continued to demonstrate elevated α-Gal A up to 28 weeks post ERT withdrawal

# STAAR and LTFU: plasma α-Gal A activity sustained over time in each cohort



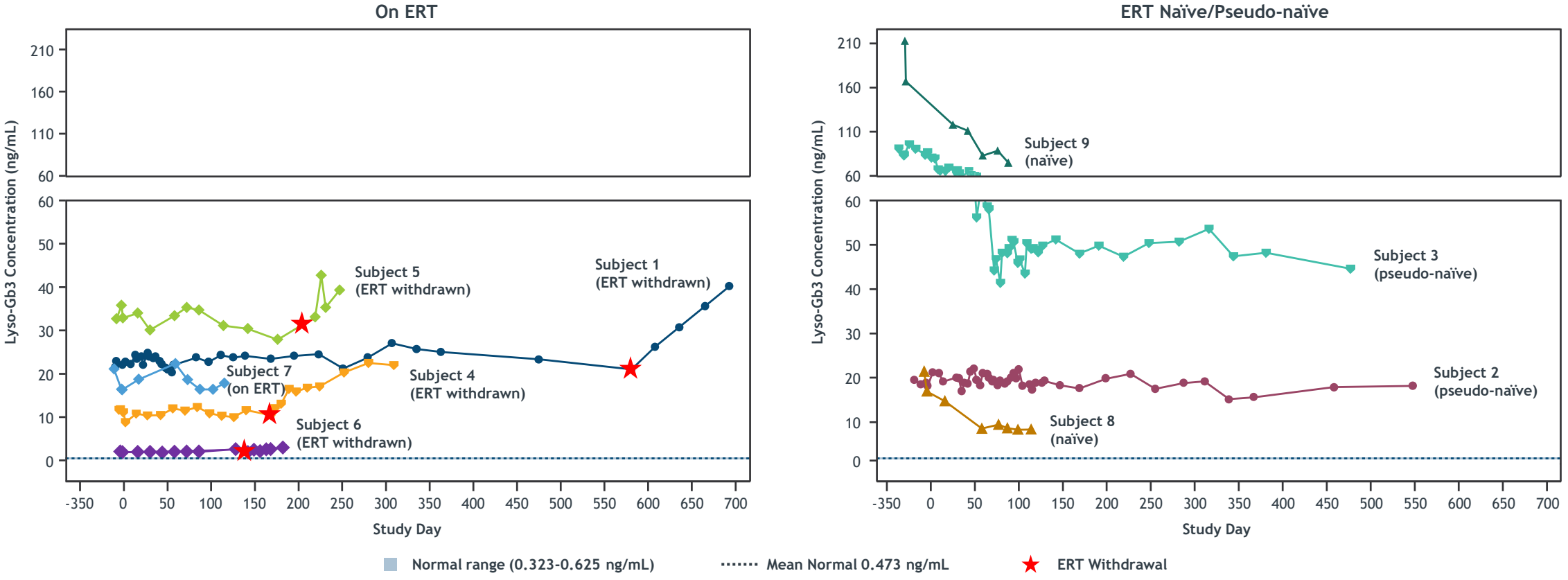

α-Gal A activity increased rapidly after dosing and remained elevated until the last sampling timepoint

All subjects exhibited above normal levels of α-Gal A activity by 5 weeks after dosing

α-Gal A activity remained elevated and above normal after ERT withdrawal

Data presented as of the cutoff date of July 21, 2022. α-Gal A activity was measured using a 3-hour reaction time and is presented in nmol/h/mL. For Subjects on ERT, sampling was at ERT trough. Normal range and mean were determined based on healthy male individuals.α-Gal A, alpha galactosidase A; ERT, enzyme replacement therapy; LTFU, long-term follow-up

# STAAR and LTFU: high lyso-Gb3 concentrations in plasma at baseline decreased after ST-920 dosing




- Two subjects exhibited substantially higher levels of plasma lyso-Gb3 pre-treatment:
  - Subject 3 (pseudo-naïve) showed an approx. 40% reduction from baseline within 10 weeks of dosing, maintained through Month 15
  - Subject 9 (naïve) showed an approx. 55% reduction from baseline within 14 weeks of dosing
- Several subjects experienced some increases in plasma lyso-Gb3 levels after ERT withdrawal. In these subjects, α-Gal A activity remained elevated, and no subject has resumed ERT

Data presented as of the cutoff date of July 21, 2022. Lyso-Gb3 was measured in plasma and is presented in concentrations (ng/mL). Normal range and mean were determined based on healthy male individuals.
Lyso-Gb3, globotriaosylsphingosine; approx., approximate; α-Gal A, alpha galactosidase A; ERT, enzyme replacement therapy; LTFU, long-term follow-up

# Conclusions

- Isaralgagene civaparvovec (ST-920) continues to be generally well tolerated; no serious treatment-related adverse events (TRAEs); no steroid treatment was required.
- Elevated α-Gal A activity was maintained through the last sampling point for all 9 subjects in all 4 dose escalation cohorts, up to 23 months for the longest treated subject.
- Subjects withdrawn from ERT exhibited elevated, sustained α-Gal A activity after ERT withdrawal for up to 28 weeks.
- Subjects with substantially higher levels of plasma lyso-Gb3 pre-treatment showed 40-55% reduction from baseline after ST-920 dosing.
- The Phase 1/2 STAAR study is ongoing and has progressed into the expansion phase, with four patients dosed.
- Based on these data, Phase 3 planning has been initiated.

Sangamo THERAPEUTICS

# Acknowledgments

**Study authors:** Patrick Deegan,[1] Jaya Ganesh,[2] Ozlem Goker-Alpan,[3] Robert J. Hopkin,[4] John Bernat,[5] William Wilcox,[6] Liching Cao,[7] Michael Chen,[7] Lisa H. Shiue,[7] Emma Bowden,[7] Sravan Jaggumantri,[7] Cristobal Passalacqua,[7] Bernard Souberbielle,[7] Bettina M. Cockroft[7]

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