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

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Introduction

Fabry Disease

- 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 globotriaosylsphingosine (lyso-Gb3)
- Nephropathy and cardiomyopathy are frequent and major complications that can lead to premature death. Enzyme replacement therapy (ERT) requires repeated intravenous (IV) infusions, which impact patient safety and quality of life
- Evidence-based recommendations promote starting ERT early in the disease course for the greatest therapeutic benefit. Despite treatment, patients may still experience disease progression and organ damage[1]

Isaralgagene Civaparvovec (ST-920), the STAAR Study, and Long-term Follow-up

- ST-920 is an investigational gene therapy using a recombinant AAV2/6 vector containing human *GLA* cDNA, which is designed to produce continuous, liver-specific expression
- STAAR is an ongoing, first-in-human, phase 1/2 clinical study evaluating the safety, tolerability, and preliminary efficacy of ST-920 in the dose escalation and expansion phases. After follow-up for 52 weeks in STAAR, participants are invited to transition into a 4-year, long-term follow-up (LTFU) study
- ST-920 is administered as a one-time IV infusion. Expression in the liver of the functional *GLA* gene results in synthesis of normal α-Gal A and release into the bloodstream. The constant production of α-Gal A is predicted to lead to a reduction and clearance of pathological Fabry disease substrates such as lyso-Gb3 in plasma and Gb3 from target organs

Methods

Study Design

- STAAR (ST-920-201) is a phase 1/2 dose-ranging, single-dose, open-label, multicenter study to assess the safety and tolerability of ST-920 in adults (aged ≥18 years) with Fabry disease (NCT04046224) in a dose-escalation phase and an expansion phase
- On study day 0, participants receive a single IV dose of ST-920 and are followed for 52 weeks. Participants who are on stable ERT may withdraw from ERT after ST-920 dosing in a controlled and monitored fashion. Upon completion of the STAAR study, participants are offered enrollment in the LTFU study (NCT05039866)
  - Dose escalation was performed in 4 cohorts across a dose range of 0.5×10^{13} to 5×10^{13} vg/kg. Safety and efficacy data of each cohort were reviewed by a safety monitoring committee prior to dose escalation
  - The expansion phase, dosing at 5×10^{13} vg/kg, comprises the following 5 cohorts: (1) α-Gal A antibody–positive males; (2) α-Gal A antibody–negative males; (3) females; (4) cardiac disease (males and females); (5) renal disease (males and females)
- Entry criteria include participants aged ≥18 years who are on ERT treatment, or are ERT naïve, or are ERT pseudo-naïve (no ERT for ≥6 months)
- The primary objective for the trial is safety and tolerability of ST-920
- Other key objectives include α-Gal A activity and lyso-Gb3 response, discontinuation of ERT, preliminary evidence of efficacy (renal function and Gb3 inclusions; cardiac function and left ventricular hypertrophy), and patient-reported outcomes (quality of life)

Results

Baseline Characteristics (Table 1)

- The Fabry Outcome Survey (FOS) is an international disease registry that has been collecting longitudinal data since 2001 on patients with a confirmed diagnosis of Fabry disease. The Fabry Outcome Survey-Mainz Severity Score Index (FOS-MSSI) is a validated age- and sex-adjusted scoring system enabling comparisons of disease severity between different patient subgroups, irrespective of age or sex. It consists of general, neurologic, cardiovascular, and renal components, which are combined to calculate the total FOS-MSSI score. Scores ≤18 are considered mild, 19-38 moderate, and >38 severe[2]
- Participants in the dose escalation phase are representative of men with classic Fabry disease. Dose escalation and expansion phase participants treated with ST-920 generally have mild or moderate disease severity

Table 1. Baseline Characteristics

					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
Dose Escalation	Cohort 1 0.5×10^{13} vg/kg	1	48	Agalsidase beta	Moderate	30.5	6.5	7	13	4	G261D	26 M
	Cohort 2 1×10^{13} vg/kg	2	25	Pseudo-naïve	Mild	12	4	8	0	0	T141I	25 M
		3	42	Pseudo-naïve	Moderate	20.5	8.5	9	3	0	W340R	21 M
	Cohort 3 3×10^{13} vg/kg	4	22	Agalsidase beta	Mild	10	4	6	0	0	S297Y	17 M
		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} vg/kg	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
Expansion	Cardiac	12	67 Female	Agalsidase beta	Mild	17.5	5.5	3	9	0	D266N	4 W
	α-Gal A Ab+ Males	10	34	Pseudo-naïve	Moderate	32.5	7.5	7	14	4	N34S	10 W
		11	49	Agalsidase beta	Moderate	28	1.2	9	3	4	Y134S	9W
		13	38	Agalsidase beta	Mild	17.5	6.5	5	6	0	A348GfsX27 insertion	2 W

Data cut-off date: October 20, 2022.
FOS-MSSI Total Score Classification: Mild ≤18; Moderate = 19-38; Severe >38.
α-Gal A, alpha galactosidase A; Ab, antibody; ERT, enzyme replacement therapy; FOS-MSSI, Fabry Outcome Survey Mainz Severity Score Index; M, months; Max, maximum; W, weeks.

Safety and Tolerability (Data Cut-off Date: October 20, 2022)

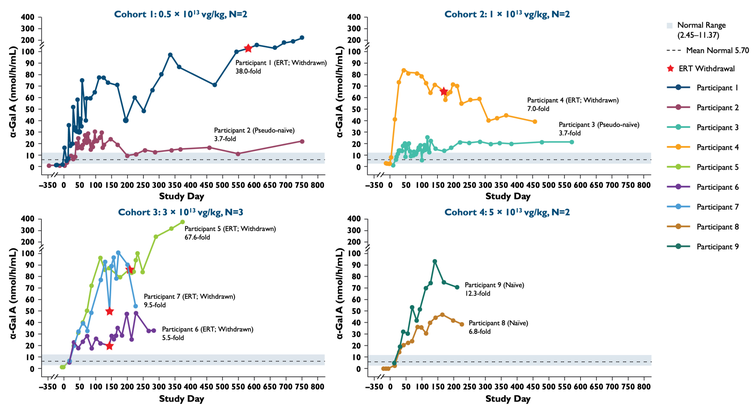
- ST-920 continues to be generally well tolerated with a favorable safety profile
  - No requirement for prophylactic corticosteroids or other immune-modulating agents
  - No cardiac events or clinically meaningful decreases in platelets have been observed
  - One expansion phase participant experienced a Grade 1 allergic reaction treated with diphenhydramine
- A total of 30 treatment-related adverse events (TRAEs) occurred in 10 of 13 (77%) participants from the dose escalation and expansion phases. All TRAEs were Grade 1 or Grade 2, with the most common being pyrexia, headache, chills, and Fabry disease (increased pain).
- As of the cut-off date, no treatment-related serious adverse events were observed

Results (cont.)

Expression of α-Gal A Activity in Dose Escalation Cohorts (Figure 1)

- Rapid and predictable increases in α-Gal A activity were observed in all participants 4–8 weeks after ST-920 dosing at the November 15, 2022, cut-off date. Sustained supraphysiological α-Gal A activity ranging from nearly 4-fold to nearly 67-fold of mean normal was observed for all 9 participants in the dose escalation phase for over 2 years for the longest-treated participant
- **ERT Withdrawal:** All 5 participants in the dose escalation phase who began the study on ERT (#1, #4–#7) have been successfully withdrawn from ERT, continued to demonstrate supraphysiological levels of α-Gal A activity following withdrawal, and have not required the resumption of ERT treatment
- **Naïve/Pseudo-naïve:** 4 participants were pseudo-naive (#2, Cohort 1 and #3, Cohort 2) or naïve (#8 and #9, Cohort 4). Cohort 4 participants achieved higher α-Gal A activity than participants dosed at lower doses. ST-920 expression observed was durable, with α-Gal A activity at supraphysiological levels maintained in all participants

Figure 1. Dose Escalation Phase α-Gal A Activity

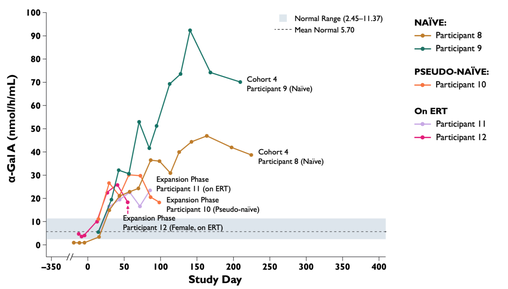


Data cut-off date: November 15, 2022.
Plasma α-Gal A activity measured using 3-hour reaction time. Normal range determined in healthy males. Fold change from normal mean was calculated at last measured time point. Long-term follow-up data: data points > Study Day 365.
α-Gal A, alpha galactosidase A;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

α-Gal A Activity in Cohort 4 and Expansion Phase Participants (Target Dose: 5×10^{13} vg/kg) (Figure 2)

- Five participants (#8–#12) have been monitored for a sufficient time period to assess the characteristics of α-Gal A expression. The highest dose (5×10^{13} vg/kg) produced rapid, predictable, and durable increases in plasma α-Gal A activity in these participants (data cut-off date: November 15, 2022). Participant #13 increased to within normal range at 4 weeks of dosing (not shown in Figure 2)
- The female participant demonstrated a similar response profile to male participants as of the cut-off date (#12, expansion phase)

Figure 2. Cohort 4 and Expansion Phase α-Gal A Activity



Data cut-off date: November 15, 2022.
Participant 13 (expansion phase): 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.

Lyso-Gb3 in Dose Escalation and Expansion Phase Participants (Figures 3 and 4)

- **Figure 3:** Where baseline levels of lyso-Gb3 started high (>80 ng/mL), participants experienced a 40% to 65%* reduction in plasma levels (#3, Cohort 2; #9, Cohort 4; #10, expansion). For the first time, and at the high dose (5×10^{13} vg/kg), we observed a further reduction in lyso-Gb3 (54%) where baseline plasma levels started lower (<25 ng/mL) (#8, Cohort 4). Plasma lyso-Gb3 continued to decrease in two participants (#9, Cohort 4; #10, expansion). Plasma lyso-Gb3 levels were stable up to 25 months (data cut-off October 20, 2022)
- **Figure 4:** In the dose escalation phase, ERT withdrawal was successful in all ERT-treated participants (#1, #4–#7). Lyso-Gb3 levels following ERT withdrawal remained within the range of levels and variability normally observed in participants treated with ERT.[1-5] In these participants, α-Gal A activity remained elevated, and no participant has experienced symptoms requiring the resumption of ERT. In the expansion phase participants (#11, #12), ERT withdrawal had not yet been initiated (data cut-off October 20, 2022)

Figure 3. Plasma Lyso-Gb3 in Naïve and Pseudo-Naïve Participants From Dose Escalation and Expansion Phases

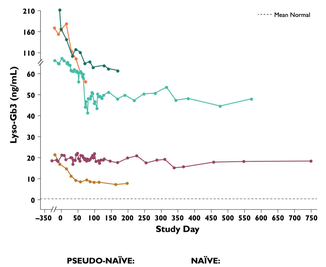
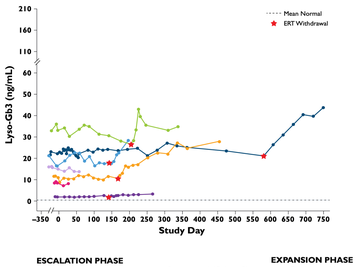


Figure 4. Plasma Lyso-Gb3 in ERT-Treated Dose Escalation and Expansion Phase Participants



Data cut-off date: October 20, 2022.
Participant 13 (expansion phase): week 2, 34.5 ng/mL. Lyso-Gb3 normal range determined in healthy males and females. Normal range for males and females combined is 0.32 to 0.63 ng/mL. Long-term follow-up data: data points > study day 365.
ERT, enzyme replacement therapy; lyso-Gb3, globotriaosylsphingosine. *The time point immediately preceding ST-920 administration was presented as the baseline value and used to calculate percent reduction.

SF-36 General Health Domain in Dose Escalation Phase Participants

- The SF-36 is the best validated and most widely used generic questionnaire to comprehensively evaluate health-related quality of life. The 36 items assess 8 health-related domains (physical function, physical role, bodily pain, general health, vitality, social function, emotional role, and mental health) that are summarized by the Physical Component score and the Mental Component score
- Studies of cross-sectional differences between clinically defined patient groups have suggested a 3- to 5-point change on any SF-36 score as minimally clinically important difference[6]
- As of the data cut-off date of October 20, 2022, participants in the dose escalation phase demonstrated a clinically meaningful and statistically significant increase in mean general health scores, as measured by the SF-36 General Health survey. The average improvement from baseline for this domain score demonstrated a statistically significant (mean = 19.6; 95% CI: 7.8, 31.4; p=0.010 [paired t-test]) and clinically meaningful change at week 52, further demonstrating the important potential efficacy of ST-920 in treating the symptoms of Fabry disease

Kidney Biopsy and Podocyturia

- Clearance or stabilization of renal Gb3 inclusions along with reductions in urine podocyte loss for the two naïve participants in cohort 4 suggest a favorable impact on progression of Fabry nephropathy and tissue absorption. (Refer to the WORLD*Symposium* platform presentation for additional details, available at the QR code above).

Conclusions

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, sustained 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

References

1. Biegstraaten M, Arngrímsson R, Barbey F, et al. *Orphanet J Rare Dis.* 2015;10:36. 2. Whybra C, Bähner F, Baron K. In: Mehta A, Beck M, Sunder-Plassmann G, eds. *Fabry Disease: Perspectives from 5 Years of FOS.* Oxford: Oxford PharmaGenesis; 2006. 3. Arends M, Biegstraaten M, Wanner C, et al. *J Med Genet.* 2018;55(5):351-358. 4. Nowak A, Beuschlein F, Sivasubramaniam V, Kasper D, Warnock DG. *J Med Genet.* 2022;59(3):287-293. 5. Krämer J, Lenders M, Canaan-Kühl S, et al. *Nephrol Dial Transplant.* 2018;33(8):1362-1372. 6. Arends M, Hollak CE, Biegstraaten M. *Orphanet J Rare Dis.* 2015;10:77.

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