An Open-label, Phase 1/2 Trial of Gene Therapy 4D-310 in Adult Males with Fabry Disease

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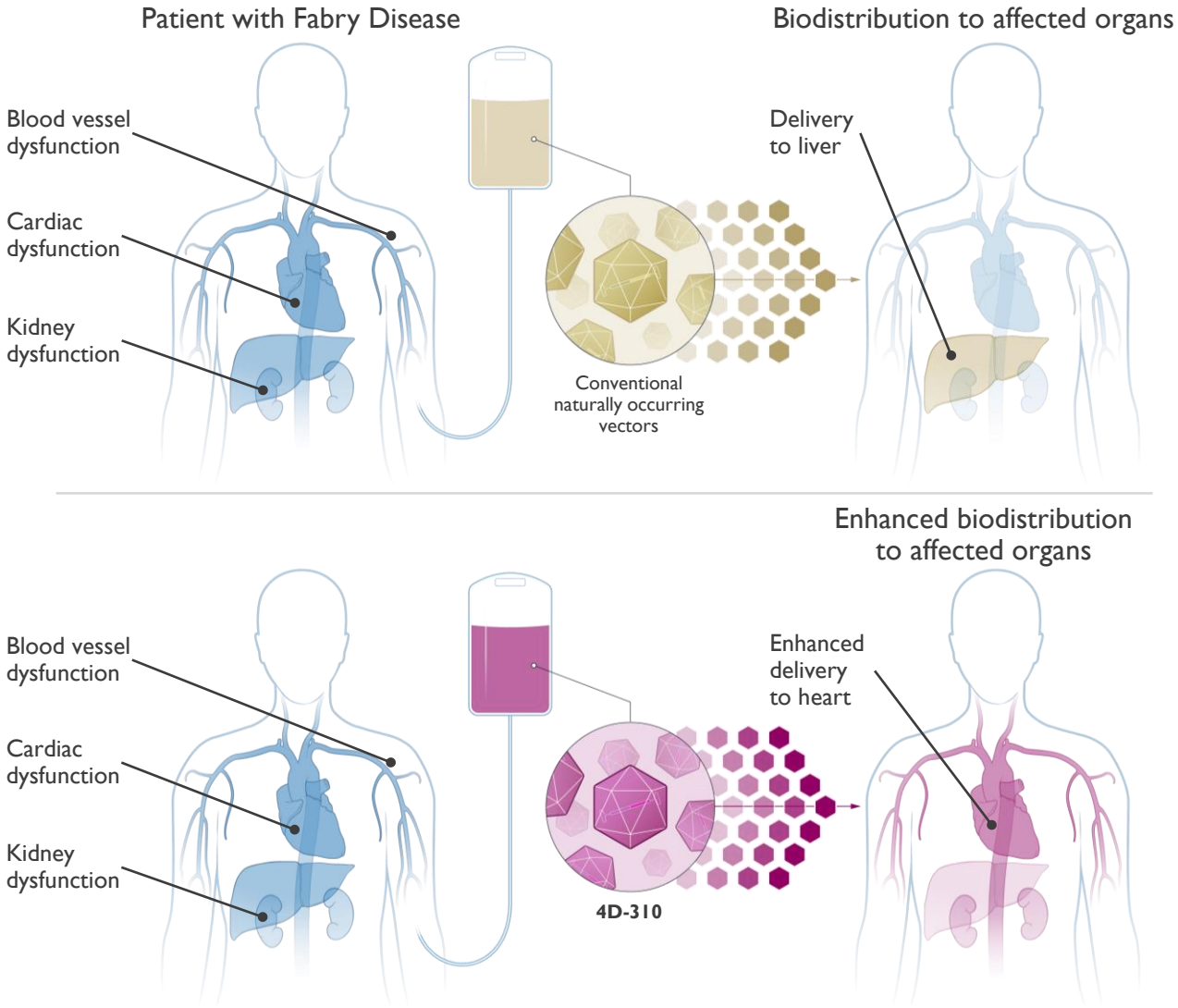
4D-310 Product Design: Unique Dual Mechanism-of-Action

INVENTED FOR LOW DOSE IV DELIVERY TO TARGET ORGANS INCLUDING HEART & HIGH SERUM AGA

PRODUCT DESIGN

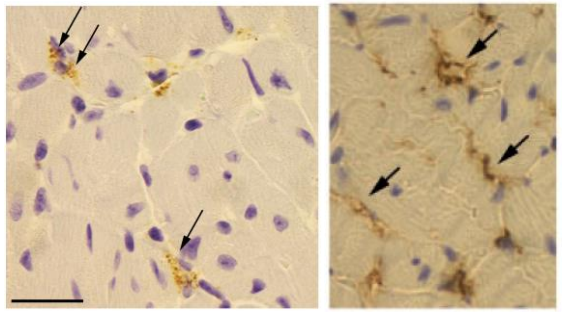
- **Vector:** C102 – Targeted & Evolved AAV
- **Transgene:** *GLA* (encodes AGA enzyme)
- **Promoter:** Ubiquitous



4D-310 Widespread AGA Gene Expression in Fabry Disease Target Organs

NHP & FABRY MOUSE AGA IMMUNOHISTOCHEMISTRY (IHC) & IN SITU HYBRIDIZATION (ISH)

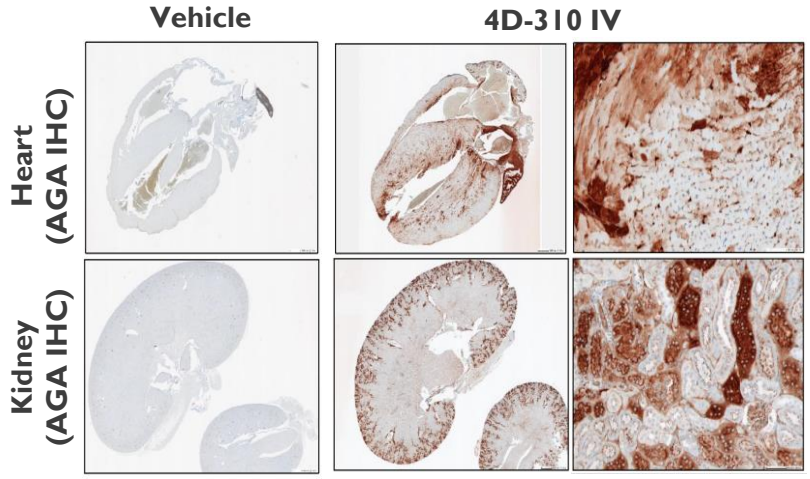
ERT & Liver-directed AAV – No AGA in Cardiomyocytes: Fabry Mice



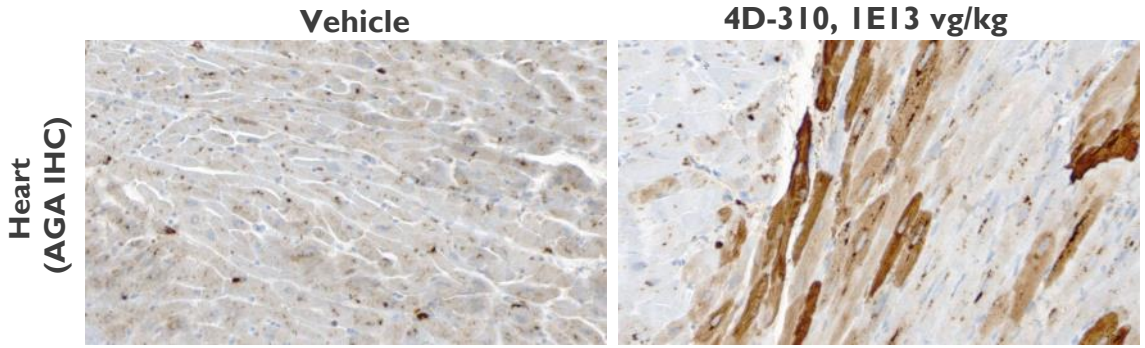
ERT (1mg/kg) | Liver-directed AAV GT

JIMD 2016;39:293;
HMG 2017;26:1182

4D-310 AGA Expression in Heart & Kidney: Fabry Mice

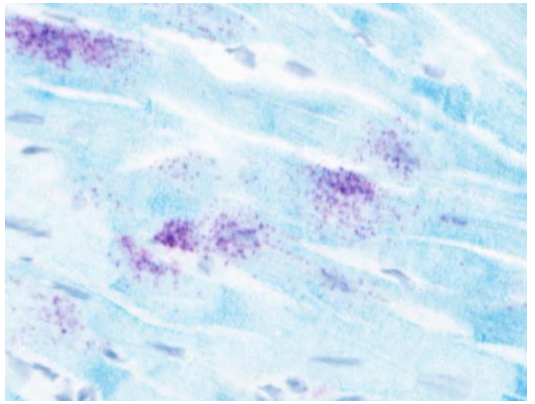


4D-310 AGA in Heart: Non-human Primates



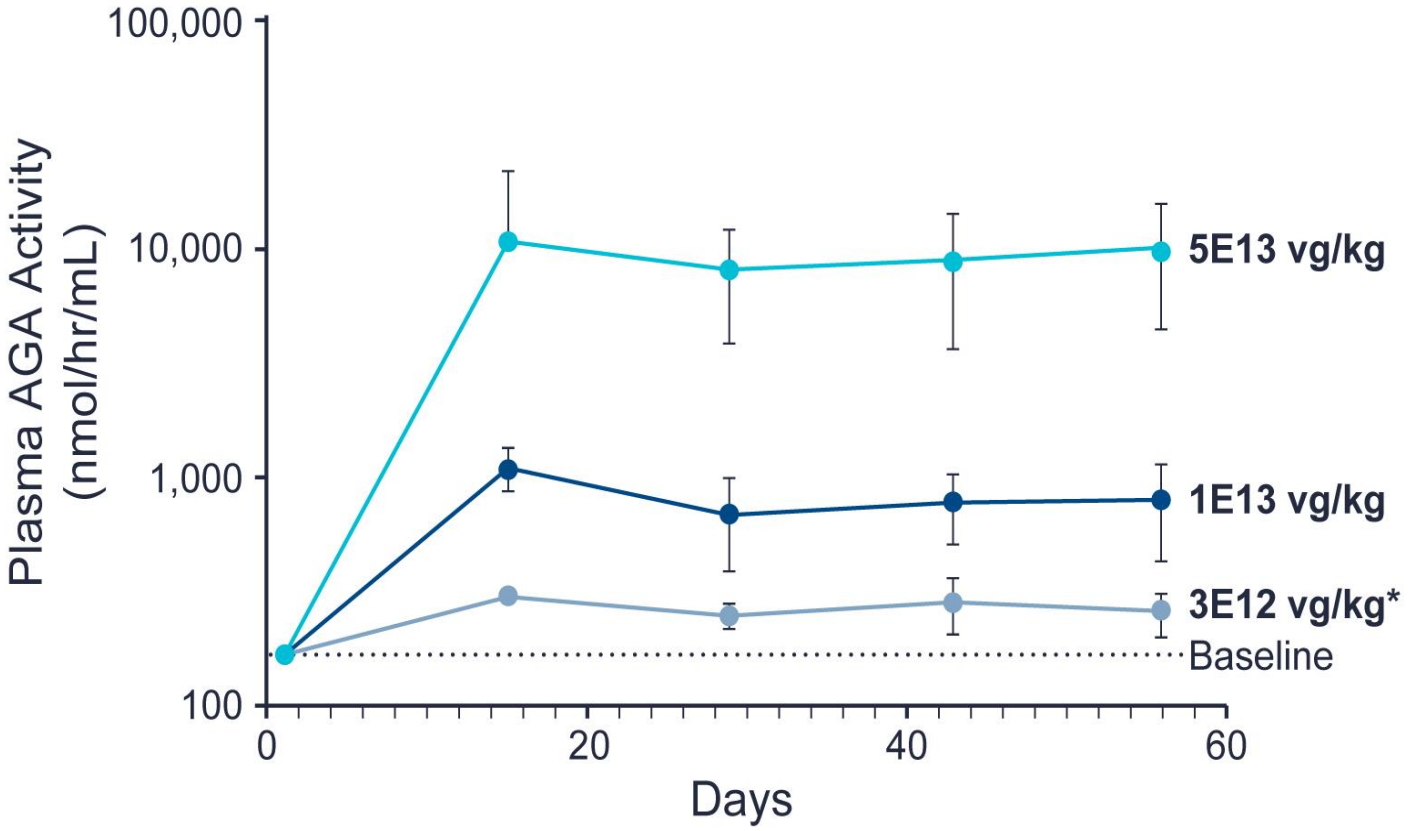
AGA transgene expression in NHP cardiomyocytes:

- Cardiac Troponin I (IHC; teal)
- 4D-310 AGA mRNA (ISH; purple)



4D-310 AGA Plasma Activity in Non-human Primates (NHPs)

DOSE-DEPENDENT STABLE AGA ACTIVITY IN PLASMA OF CYNOMOLGUS MONKEYS



70-fold over baseline level

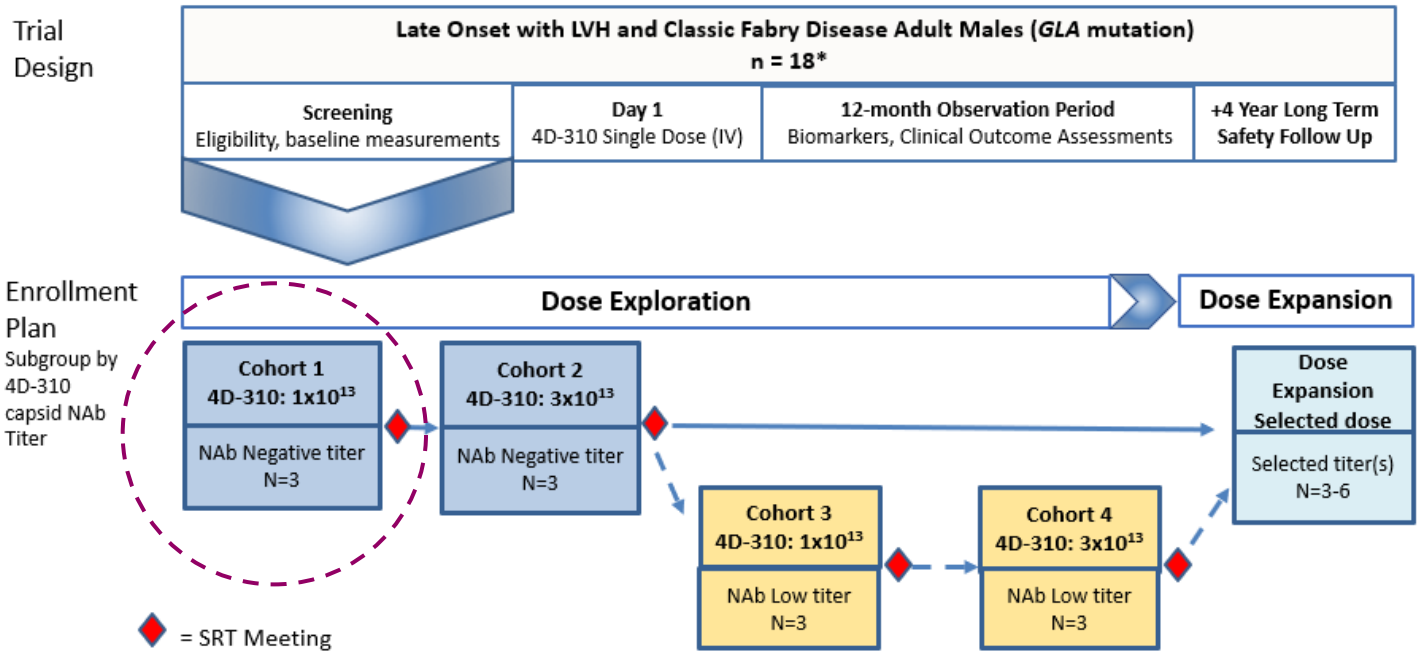
3.4-fold over baseline level

1.9-fold over baseline level

*One NHP in the low dose cohort has been excluded from the dataset as a positive statistical outlier as it exhibited AGA activity that was 66 to 124 standard deviations higher than the average of other NHPs treated with low dose 4D-310

4D-310 Study Design: Broad Enrollment Criteria

OPEN-LABEL, PHASE 1/2 TRIAL IN ADULTS WITH FABRY DISEASE



Dashed arrow = optional arm if low titer subjects identified

*n=maximum of 42 subjects if DLTs are observed and subjects are added to cohorts to provide additional safety information and/or confirm the selected dose

KEY INCLUSION CRITERIA

- Males ≥ 18 years of age
- Pathogenic *GLA* mutation
- Classic **OR** Late-onset FD with LVH
- ERT-On, ERT-Off **OR** ERT-naïve
- Anti-AGA Ab status positive **OR** negative**

KEY EXCLUSION CRITERIA

- High titer 4D-310 NAb
- eGFR <45 mL/min/1.73m2
- LVEF <45% (Echo)

PRIMARY ENDPOINT

- Incidence & severity of adverse events

KEY SECONDARY ENDPOINT

- **Serum AGA Activity:** change from baseline

EXPLORATORY ENDPOINTS

- **Cardiac Imaging & QoL:** change from baseline

**Currently exclude anti-AGA antibody titer ≥1:25,000

Baseline Patient Characteristics

STUDY ENROLLED CLASSIC FABRY DISEASE PATIENTS WITH ANTI-AGA ANTIBODY POSITIVITY

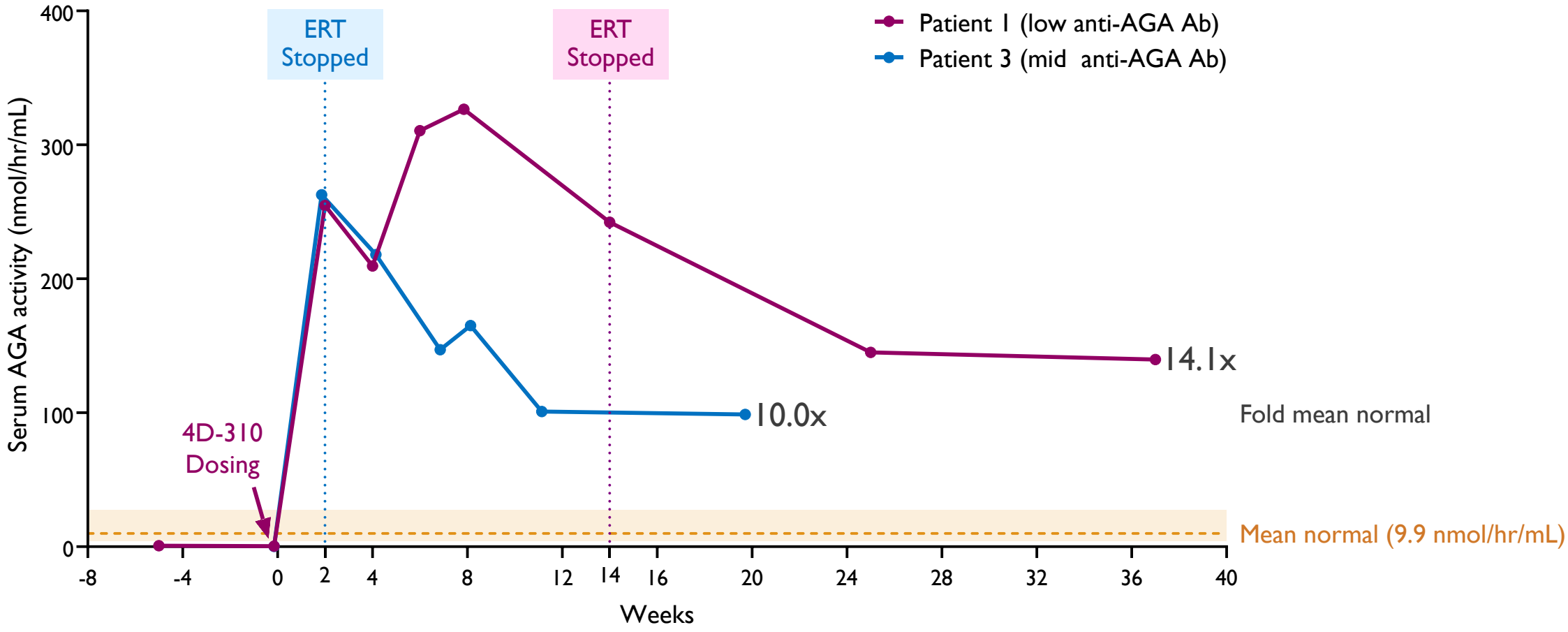
	Patient 1	Patient 2	Patient 3
Age	51 years	32 years	26 years
Race/Ethnicity	White/Hispanic or Latino	White/Not Hispanic or Latino	White/Not Hispanic or Latino
Disease classification	Classic	Classic	Classic
Mutation	c.1023A>C (p.E341D)	c.708G>T (p.W236C)	c.974G>A (p.G325D)
Serum AGA activity (nmol/hr/mL)	0.42	0.00	0.30
ERT experience	Yes	Yes	Yes
ERT status at enrollment	**ERT-ON**	**ERT-OFF**	**ERT-ON**
Serum lyso-Gb3 (ng/mL)	6.28	101.00	8.78
Anti-AGA antibody titer	**1:947 (low)**	**1:99,900 (high)**	**1:13,900 (mid)**
eGFR (mL/min/1.73m^2)	107	130	125

Reference range:

- Serum AGA activity: 4.44-27.42 nmol/hr/mL
- Serum Lyso-Gb3: ≤ 1.0 ng/mL
- eGFR: > 60 mL/min/1.73m2

Stable High-Level AGA Activity After Discontinuation of ERT: 10- to 14-Fold Mean Normal

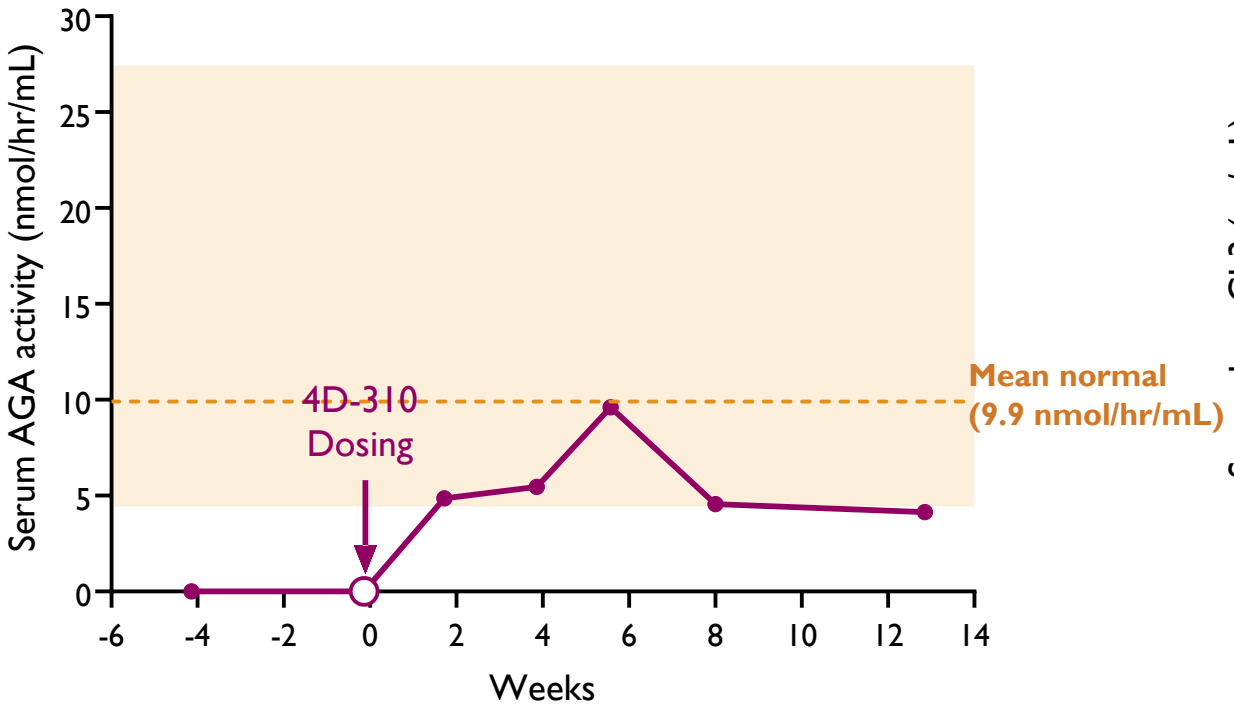
PATIENTS 1 & 3 WITH POSITIVE ANTI-AGA ANTIBODY TITERS: FOLLOW-UP 20-37 WEEKS

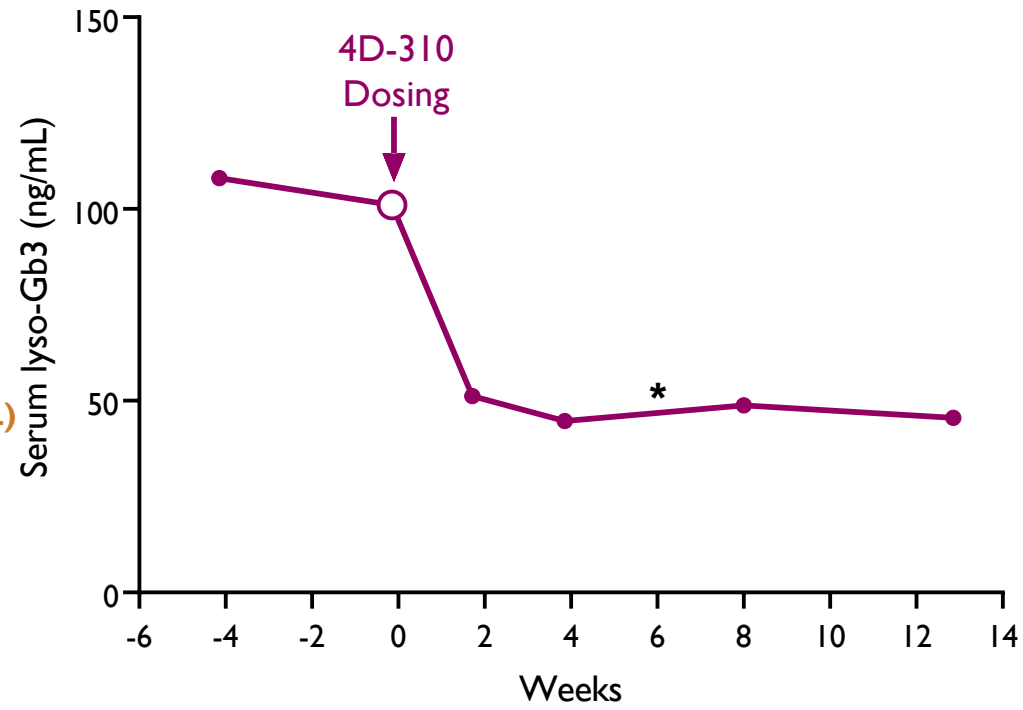


Serum AGA activity: mean normal = 9.9 nmol/hr/ml; normal range: 4.44 – 27.42 nmol/hr/mL;

Stable AGA Activity In Normal Range Despite High-Level Anti-AGA Antibody Titers

PATIENT 2 WITH HIGH ANTI-AGA ANTIBODY TITER (~1:100,000): FOLLOW-UP 13 WEEKS





BASELINE CHARACTERISTICS

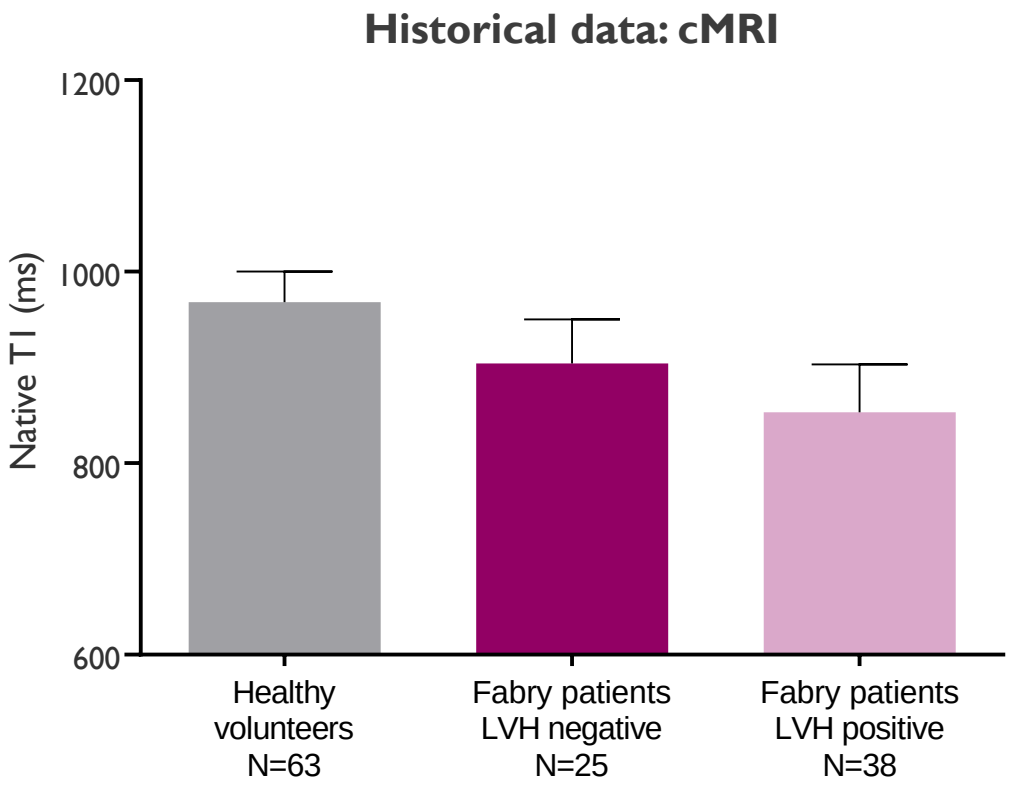
Anti-AGA Ab Status	ERT Status (lyso-Gb3)	ERT Experience
1:99,900 (24X mean normal)	ERT-**OFF;** high lyso-Gb3	Yes

Serum AGA activity: mean normal = 9.9 nmol/hr/ml; normal range: 4.44 – 27.42 nmol/hr/mL;
Lyso-Gb3 normal range: ≤ 1.0 ng/mL
* = Patient 2 week 6 lyso-Gb3 datapoint not evaluable due to hemolysis

Cardiac Imaging: MRI & Echo

ASSESSING BIOCHEMICAL COMPOSITION (SUBSTRATE ACCUMULATION) & FUNCTION (CONTRACTILITY)

- **Cardiac MRI (cMRI):**
  - Sphingolipid Accumulation: Measured by **Native T1** - decreased in Fabry disease
- **Echocardiography:**
  - Cardiac Contractility: Measured by **Global Longitudinal Strain (GLS)**
- **Central Reading Center:**
  - Duke Clinical Research Institute



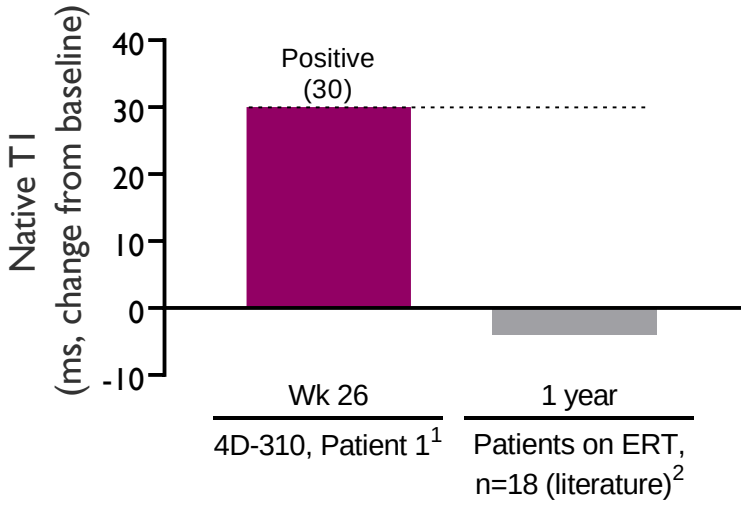
Ref: Pica et al. 2014;16:99

Cardiac Imaging (Patient 1): 6-Month Timepoint

CARDIAC MRI (cMRI) NATIVE T1 & GLOBAL LONGITUDINAL STRAIN AFTER 4D-310

cMRI Native T1

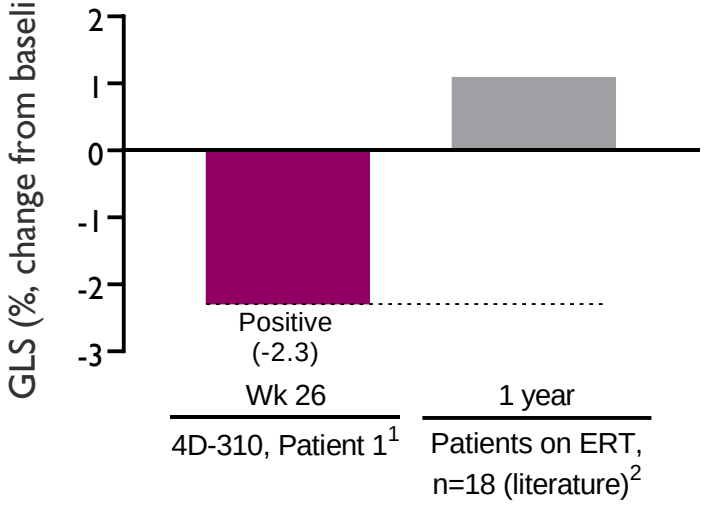
(Minimal detectable difference = 29*)



4D-310, Patient 1		Patients on ERT, n=18 (literature)	
Baseline	949.8	Baseline	916 ± 52
Wk 26	979.8	1 Year	912 ± 50

Global Longitudinal Strain (GLS)

(Minimal detectable difference = 1.5%*)



4D-310, Patient 1		Patients on ERT, n=18 (literature)	
Baseline	-16..4	Baseline	-13.2 ± 3.4
Wk 26	-18.7	1 Year	-12.1 ± 4.8

[1]Patient 1 was on ERT for 17 years prior to 4D-310 dosing

[2]Nordin et al. *Circ Cardiovasc Imaging*. 2019. Patients were on ERT with median duration of 4.2 (1.4-12.2) years

GLS (Echo, 4-chamber view), normal: ≥ -15.9%

***Minimal detectable difference (MDD):**

- Native T1: 29 ms (Altaha, *J Am Coll Cardiol Img* 2020;13:951)
- GLS: 1.5% (Lambert, *Heart* 2020;106:817)

Cardiac Quality of Life: Patient-Reported Outcomes

KCCQ SCORES 12-38 WEEKS AFTER 4D-310

Patient	Assessment Timepoint	Kansas City Cardiomyopathy Questionnaire (KCCQ) Total score range = 23-133 (higher score = less severe)
Patient 1	Day -1	121
	Wk 12	122
	Wk 26	121
	Wk 38	123 (+2)
Patient 2	Day -1	79
	Wk 12	**90 (+11)**
Patient 3	Day -1	111
	Wk 12	**116 (+5)**
Minimal clinically important difference*		**5 points**

*Reference: Spertus et al. *JACC* 2020;76:2379

Interim Safety & Tolerability Summary

MANAGEABLE SAFETY PROFILE TO DATE; 12-38 WEEKS FOLLOW UP AFTER DOSING

- 4D-310 demonstrated a manageable safety profile
- No dose-limiting toxicities
- No cardiac toxicity
- No clinically significant liver toxicity
- Patient 2 (anti-AGA Ab HIGH): single episode atypical hemolytic uremic syndrome (aHUS)
  - Transient & self-limited
  - Hospitalization for observation (resulting in SAE)
  - Discharged after 4 days: observation & hydration
  - Received no complement inhibitor & no dialysis
  - Resolved fully

aHUS-Associated Labs: 1 Pt Self-Limited and Transient aHUS

COMPLEMENT ACTIVATION RELATED LABORATORY VALUES: CTCAE GRADE

	Baseline	Day 8	Day 15	Wk 4	Wk 6	Wk 8	Wk 12	Wk 26	Wk 38
Creatinine									
Patient 1	-	-	-	-	-	-	-	-	-
Patient 3	-	-*	-	-	N.A.	-	-		
Patient 2	-	3**	2**	-	-	-	-		
Platelet count									
Patient 1	-	-	-	-	-	-	-	-	-
Patient 3	-	-	-	-	-	-	-		
Patient 2	-	2	1	-	-	-	-		

- Within normal range

*Transient Grade 2 proteinuria; Grade 1 LDH elevation; PT/PTT within normal limits; platelet within normal range (intranormal decrease); d-dimer mildly elevated; C4 complement 11 mg/dL (ref range 15-53 mg/dL)

**Patient 2 creatinine values at Days 8 & 15: 4.37 and 3.54 mg/dL, respectively.

Liver Function Labs: No Evidence of Significant Toxicity

LIVER LABORATORY VALUES: CTCAE GRADE

	Baseline	Day 8	Day 15	Wk 4	Wk 6	Wk 8	Wk 12	Wk 26	Wk 38
AST									
Patient 1	-	-	-	-	-	-	-	-	-
Patient 3	-	-	-	-	N.A.	-	-		
Patient 2	-	-	-	-	-	-	1*		
ALT									
Patient 1	-	-	-	-	-	-	-	-	-
Patient 3	-	-	-	-	N.A.	1	-		
Patient 2	-	-	-	-	-	-	1*		
Bilirubin									
Patient 1	-	-	-	-	-	1	-	-	-
Patient 3	-	-	-	-	N.A.	-	-		
Patient 2	-	-	-	-	-	-	-		

- Within normal range; *Grade 1 ALT, AST subsequently resolved

Cardiac Safety Studies: No Evidence of Toxicity

	Baseline	Wk 4	Wk 8	Wk 26
Troponin T (marker of cardiomyocyte injury)				
Patient 1	-	-	-	-
Patient 3	-	-	-	
Patient 2	-	-	-	
CK-MB (marker of cardiomyocyte injury)				
Patient 1	-	-	-	-
Patient 3	-	-	-	
Patient 2	-	-	-	
Galectin-3 (marker of matrix remodeling and inflammation)				
Patient 1	-	-	-	-
Patient 3	-	-	-	
Patient 2	-	-	-	
NT-ProBNP (marker of myocardial stretch)				
Patient 1	-	-	-	-
Patient 3	-	-	-	
Patient 2	-	1*	-	

- Within normal range; *Mild elevation (<2 ULN) associated with transient kidney insufficiency

- No evidence of adverse cardiac effects to date:
  - ECG
  - Echocardiography
  - cMRI

Summary: Ongoing 4D-310 Ph 1/2 Clinical Trial

DATA CUT-OFF DATE: 1/13/2022

- 4D-310 gene therapy has a unique **dual mechanism-of-action**
- 4D-310 demonstrated a manageable safety profile and no DLTs
- Clinical activity was observed:
  - Serum AGA activity elevated in all three patients: Mean AGA enzyme activity within, or significantly above, the normal range
  - Stable high-level AGA activity following discontinuation of ERT: 10- to 14-fold mean normal
  - Serum lyso-Gb3 substrate decreased significantly: Demonstrated in patient with elevated pre-treatment lyso-Gb3 (entered study OFF-ERT)
  - Cardiac endpoints: Preliminary clinical data suggests encouraging effects on cardiac endpoints (biochemical composition, function, QoL)
- **Phase 1/2 enrollment ongoing** in U.S. & APAC clinical trials

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