4DMT 4D-310 and 4D-110 Clinical Data Conference Call

October 25, 2021

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David Kirn, MD

Co-Founder, Chief Executive Officer

Pipeline

CLINICAL-STAGE, RARE & LARGE PATIENT POPULATIONS

VECTOR *Delivery*	PRODUCT CANDIDATE	INDICATION	LEAD OPTIMIZATION	IND-ENABLING	PHASE 1	PHASE 2	PHASE 3	PRODUCT RIGHTS
R100 *Intravitreal* 	OPHTHALMOLOGY							
	4D-125	XLRP						4DMT
	4D-110	CHM						4DMT
	4D-150	Wet AMD						4DMT
		DME						4DMT
C102 *IV* 	CARDIOLOGY							
	4D-310	Fabry Disease						4DMT
A101 *Aerosol* 	PULMONOLOGY							
	4D-710	Cystic Fibrosis						4DMT

4D-310 Phase 1/2 Trial: Initial Clinical Data

Key Takeaways for 4D-310 Clinical Data

DATA CUT-OFF DATE: 10/12/21

- 4D-310 demonstrated a manageable safety profile and no DLTs
- Clinical activity was observed in all patients at all timepoints
  - Mean AGA enzyme activity was within, or significantly above, the normal range in all three patients
  - Serum lyso-Gb3 substrate decreased significantly in patient with elevated pre-treatment lysoGb3 (entered study OFF-ERT)
  - Serum lyso-Gb3 substrate remained low following discontinuation of ERT in both patients who entered study ON-ERT

Fabry Disease Background

HIGH UNMET MEDICAL NEED IN BOTH CLASSIC AND LATE-ONSET POPULATIONS

- X-linked monogenic recessive: *GLA* mutations (AGA enzyme)
- Substrate (Gb3, lyso-Gb3): damage to kidney, heart & blood vessels
- Prevalence: ~ 19,000 US & EU-5; ~50,000-70,000 est newborn screening
- Two phenotypes:
  - Classic (~50%): <5% enzyme activity, early-onset
  - Late-onset (~50%): ~5%-20% enzyme activity, older age-onset
- Standard of care: Enzyme Replacement Therapy (ERT)
- High unmet medical need: biweekly IV dosing & lack of clear cardiac benefit
- Anti-AGA Ab induced by ERT in ~50% of patients: excluded from Gene Therapy trials

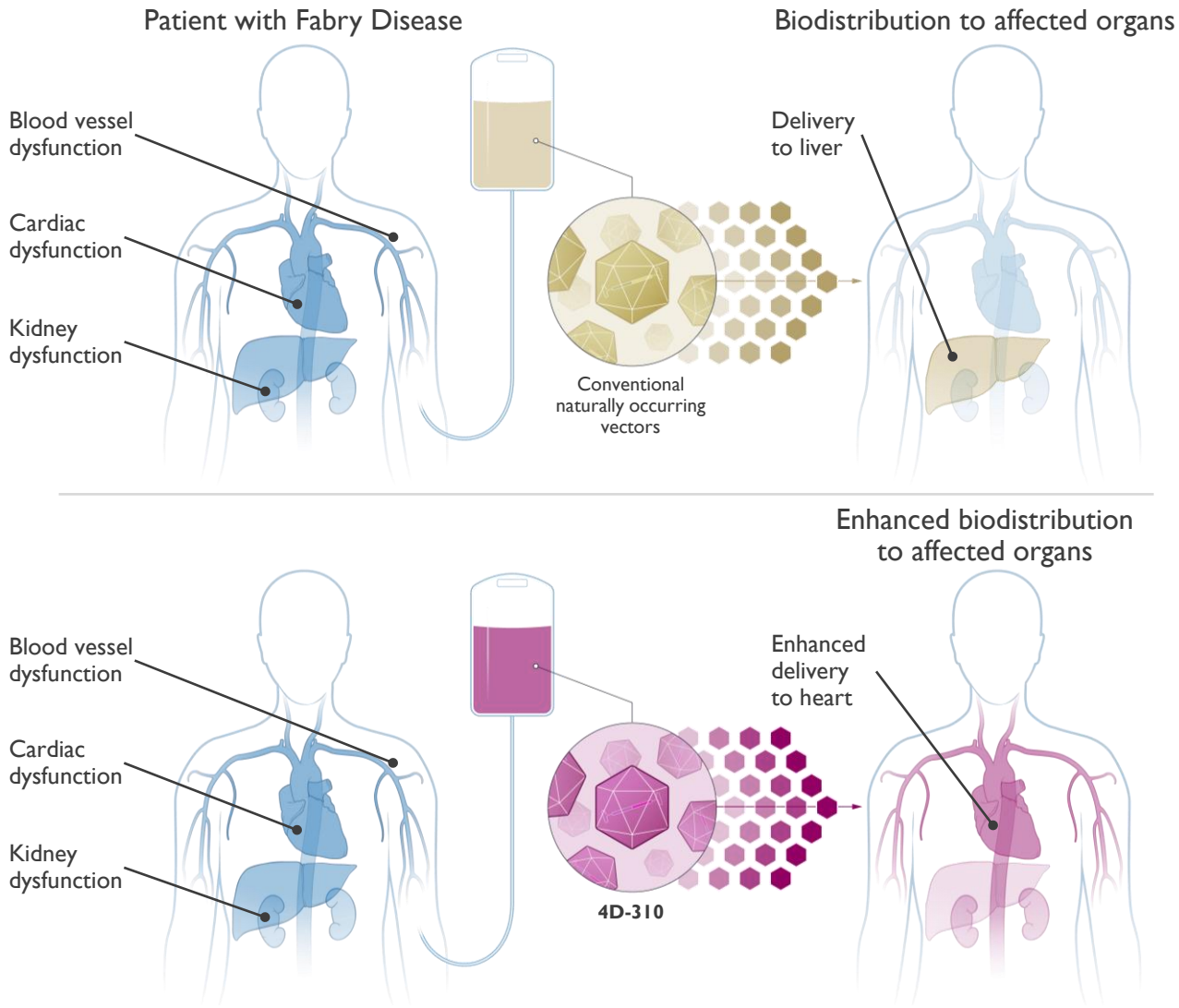
1. *Eng et al. 2001*
2. *Tsukimura et al. Mol Genet Metab Rep 2020;25:100650*

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

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

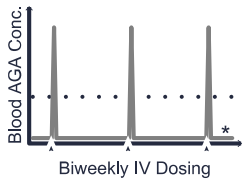
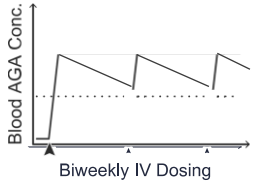
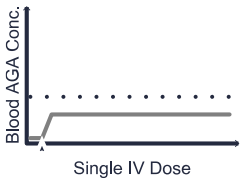
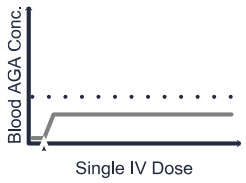
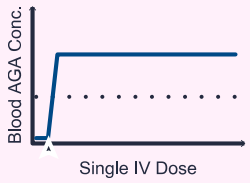
PRODUCT DESIGN

- **Vector:** C102
- **Transgene:** *GLA* (encodes AGA enzyme)
- **Promoter:** Ubiquitous



4D-310 Competitive Advantages: Dual MOA Product Design

DESIGNED FOR HIGH STABLE SERUM AGA AGA & EXPRESSION WITHIN TARGET ORGANS INC HEART

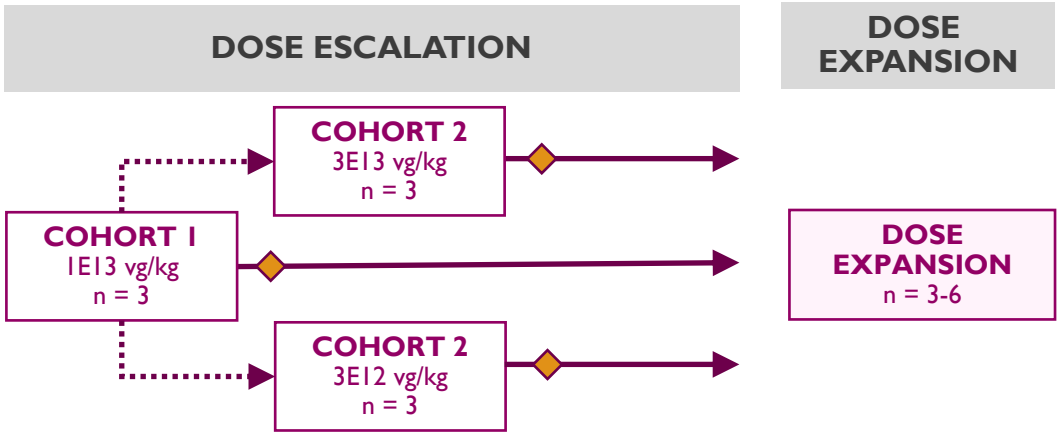
		ERT		Gene Therapy		
MOA	**Product Design**	AGA Enzyme Infusions	PEGylated AGA	Autologous Stem Cells	AAV Liver-directed	**4D-310**
AGA: **Systemic PK**	Pharmacokinetics					
	No chemotherapy/ bone marrow ablation	+	+	–	+	+
AGA: **Production in Target Cells**	Heart, Kidney, Blood Vessels	–	–	–	–	+
AGA: **Avoid Anti-AGA Ab**	Intracellular production	–	–	–	–	+

Abbreviations: Ab, antibodies; AGA, aspartylglucosaminidase; AAV, adeno-associated virus; ERT, enzyme replacement therapy; IV, intravenous; n.a., not applicable.

4D-310 Study Design: Broad Enrollment Criteria

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

STUDY DESIGN



ASSESSMENT SCHEDULE: BIOMARKERS

	Screening/Treatment Period				Observation Period										
Visit	SV1	SV2	D-1	D1	D2	D4	D8	D15	W4*	W6	W8	W12	W26	W38	W52 or ET
Visit Window (days)	Up to -180	-45 to -2	–	–	–	±1	±1	±1	±3	±3	±3	±7	±7	±7	±7
Fabry Blood Panel (AGA, lysoGb3); central lab[h]	◆	◆						◆	◆	◆	◆	◆	◆	◆	◆

◆ Biomarker Assessment (Mayo Clinic)

KEY INCLUSION CRITERIA

- Males ≥ 18 years of age
- Pathogenic *GLA* mutation
- Classic FD, 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 (>1:1,000)
- eGFR <45 mL/min/1.73m2
- LVEF <45% (Echo)

PRIMARY ENDPOINT

- Incidence & severity of adverse events

KEY SECONDARY ENDPOINTS

- Change from baseline in serum AGA activity
- Change from baseline in serum lyso-Gb3

Baseline Patient Characteristics

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

	Patient 1	Patient 2	Patient 3
Age dosed with 4D-310	51 years	32 years	26 years
Anti-AGA antibody titer	1 : 947	**1 : 99,900**	1 : 13,900
Disease classification	**Classic**	**Classic**	**Classic**
Serum AGA activity (nmol/hr/mL)	0.42	0.00	0.30
ERT experience	Yes	Yes	Yes
ERT status at enroll	**ERT-ON**	**ERT-OFF**	**ERT-ON**
Serum lyso-Gb3 (ng/mL)	**6.28**	**101.00**	**8.78**
Mutation	c.1023A>C (p.E341D)	c.708G>T (p.W236C)	c.974G>A (p.G325D)

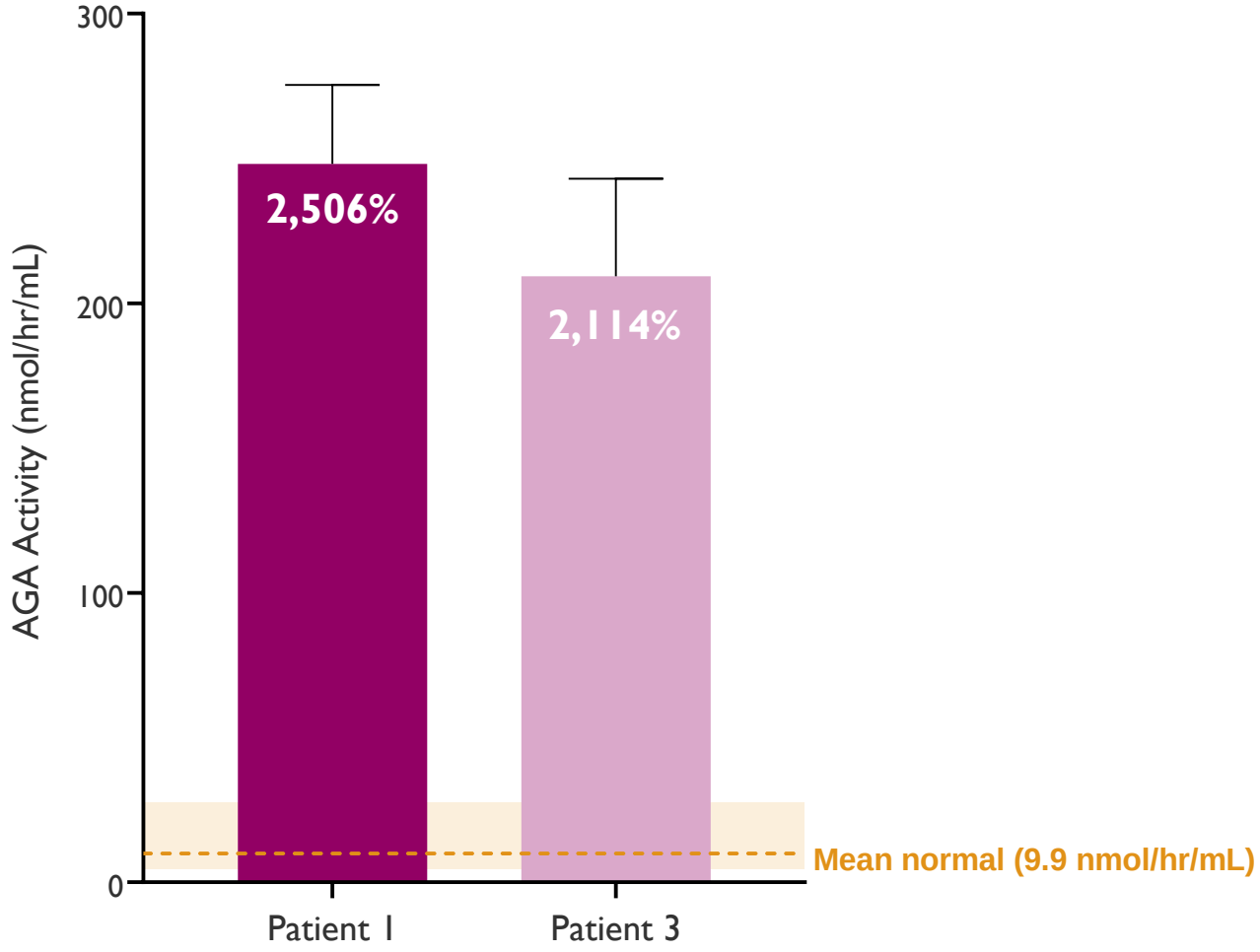
Reference range:
- Serum AGA activity: 4.44-27.42 nmol/hr/mL
- Serum Lyso-Gb3: ≤ 1.0 ng/mL

4D-310 Mean Serum AGA Activity: >20-Fold Mean Normal

AGA ANTIBODY POSITIVE LOW & MID TITERS: PATIENTS 1 & 3 AGA ACTIVITY OVER TIME

Mean Serum AGA Activity:

- Patient 1: 248.1 nmol/hr/mL
- Patient 3: 209.3 nmol/hr/mL



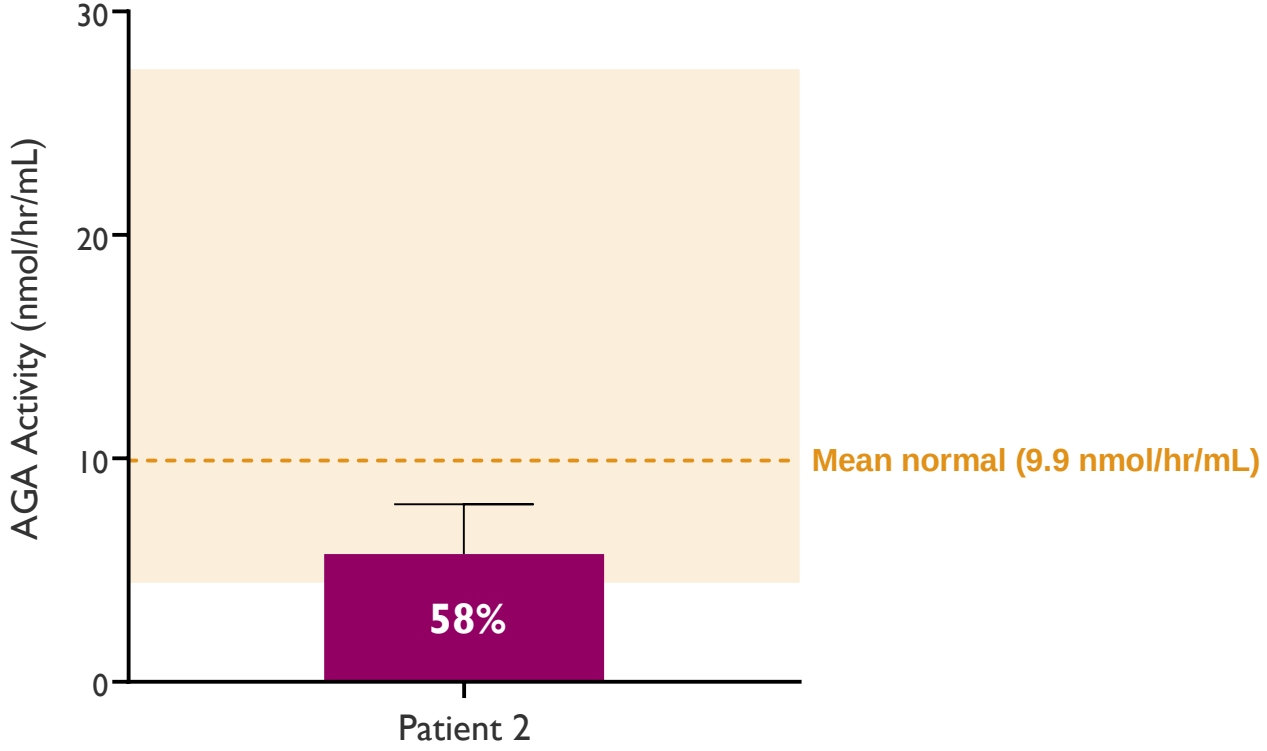
Serum AGA activity: mean normal = 9.9 nmol/hr/ml; normal range: 4.44 – 27.42 nmol/hr/mL

4D-310 Mean Serum AGA Activity: Within Normal Range

AGA ANTIBODY POSITIVE HIGHEST TITER: PATIENT 2 (HIGHEST TITER OF ALL ENROLLED & SCREENED)

Mean Serum AGA Activity:

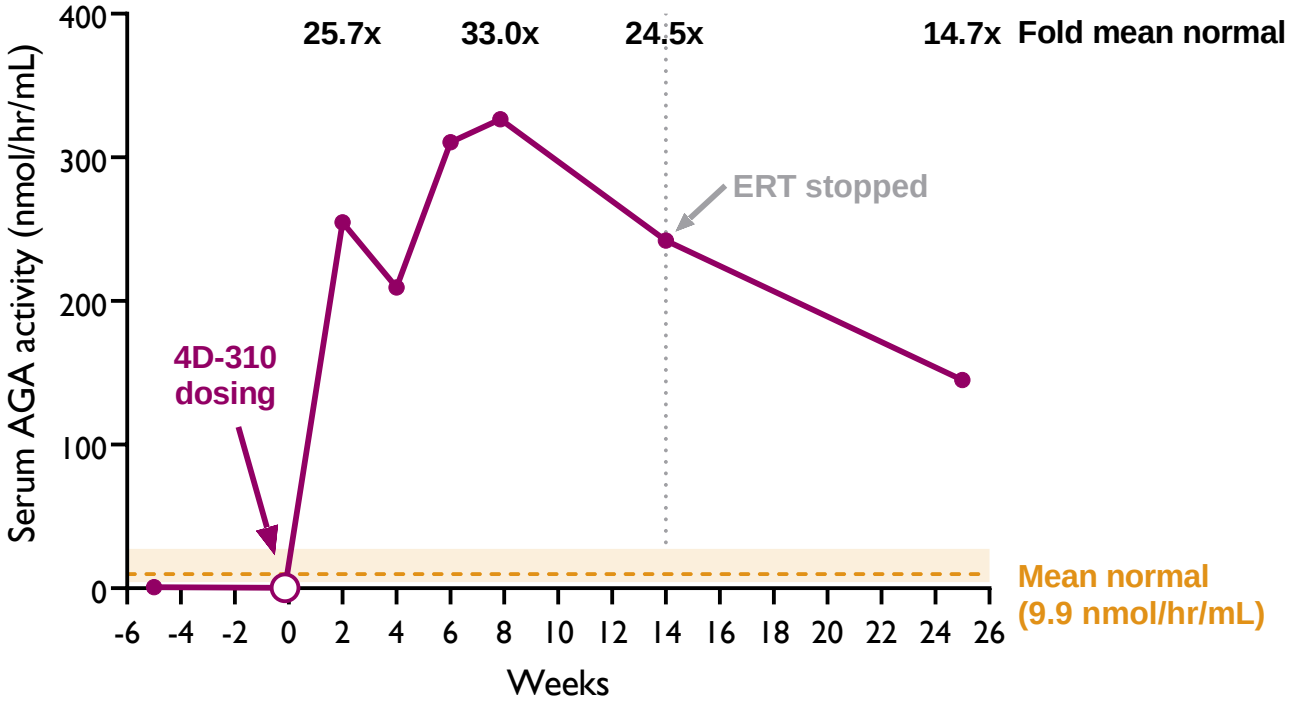
- Patient 2: 5.7 nmol/hr/mL

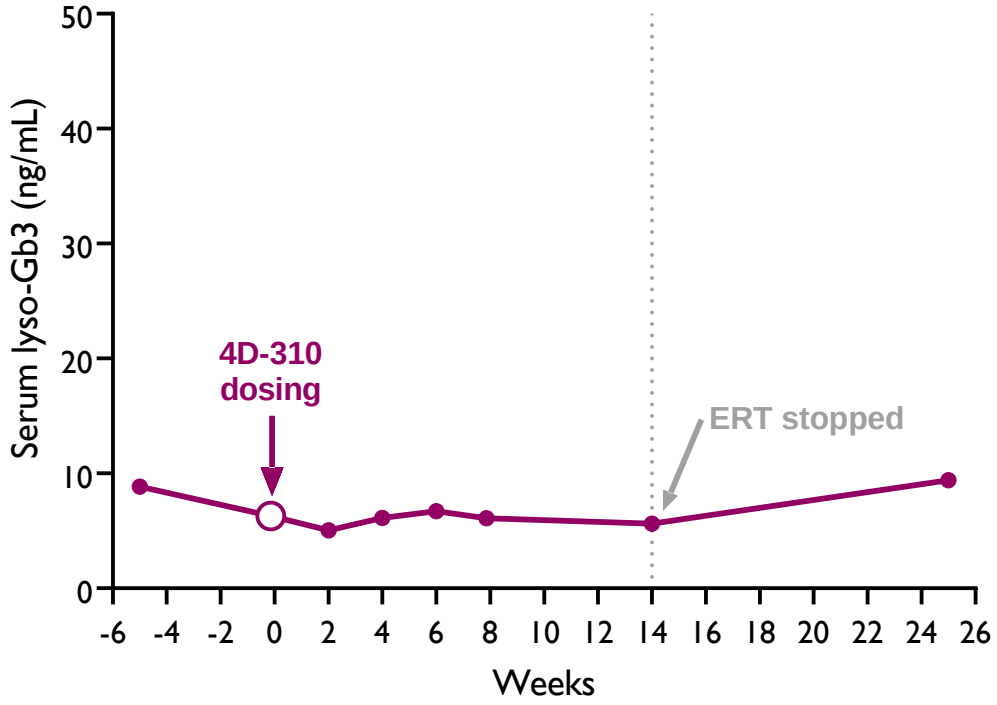


Serum AGA activity: mean normal = 9.9 nmol/hr/ml; normal range: 4.44 – 27.42 nmol/hr/mL;

Patient 1: AGA Activity & Lyso-Gb3

AGA ACTIVITY ABOVE NORMAL RANGE; LYSO-GB3 STABLE AFTER ERT WITHDRAWAL





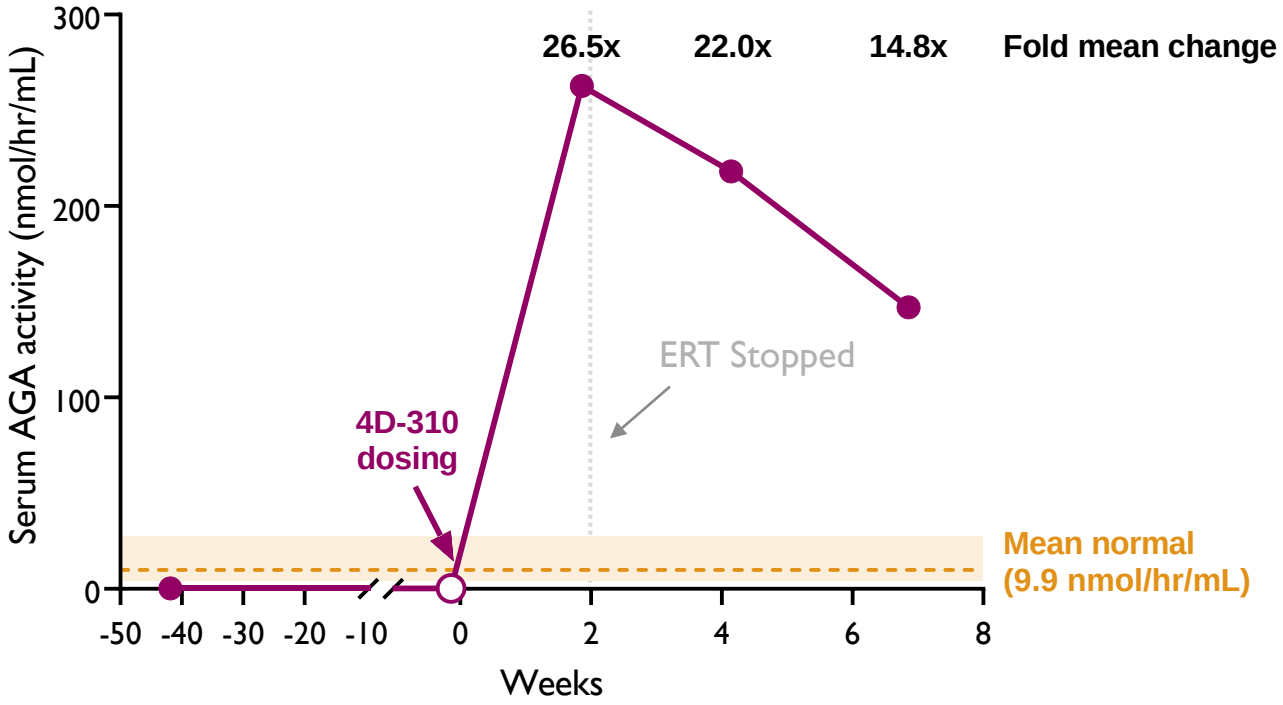
BASELINE CHARACTERISTICS

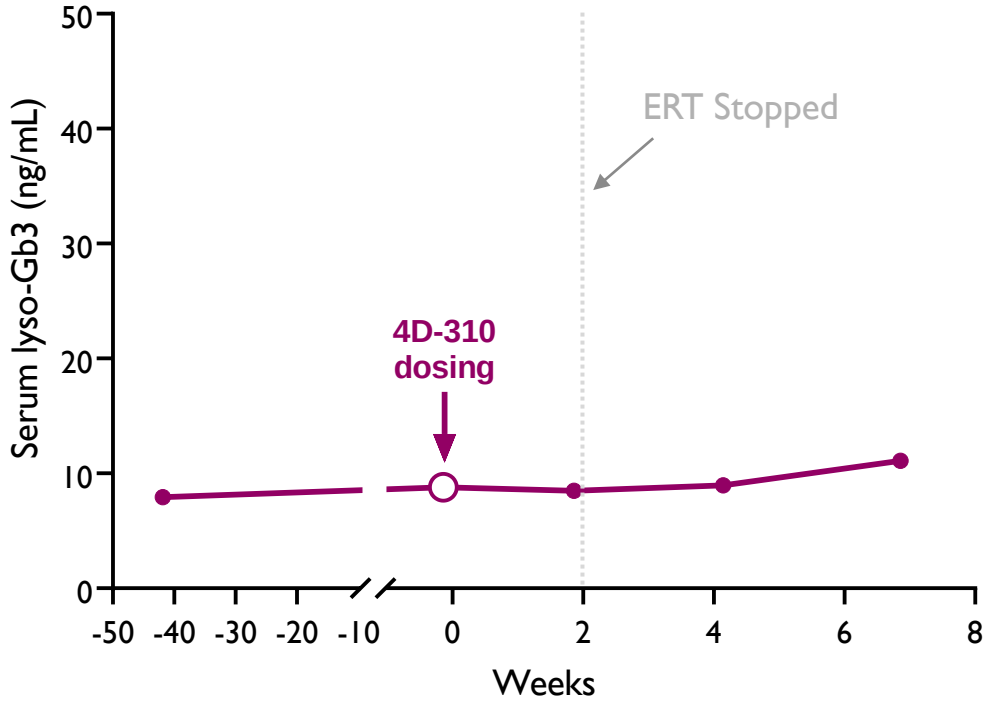
Anti-AGA Ab Status	ERT Status (lyso-Gb3)	ERT Experience
1:947	ERT-**ON;** low lyso-Gb3	Yes

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 3: AGA Activity & Lyso-Gb3

AGA ACTIVITY ABOVE NORMAL RANGE; LYSO-GB3 STABLE AFTER ERT WITHDRAWAL





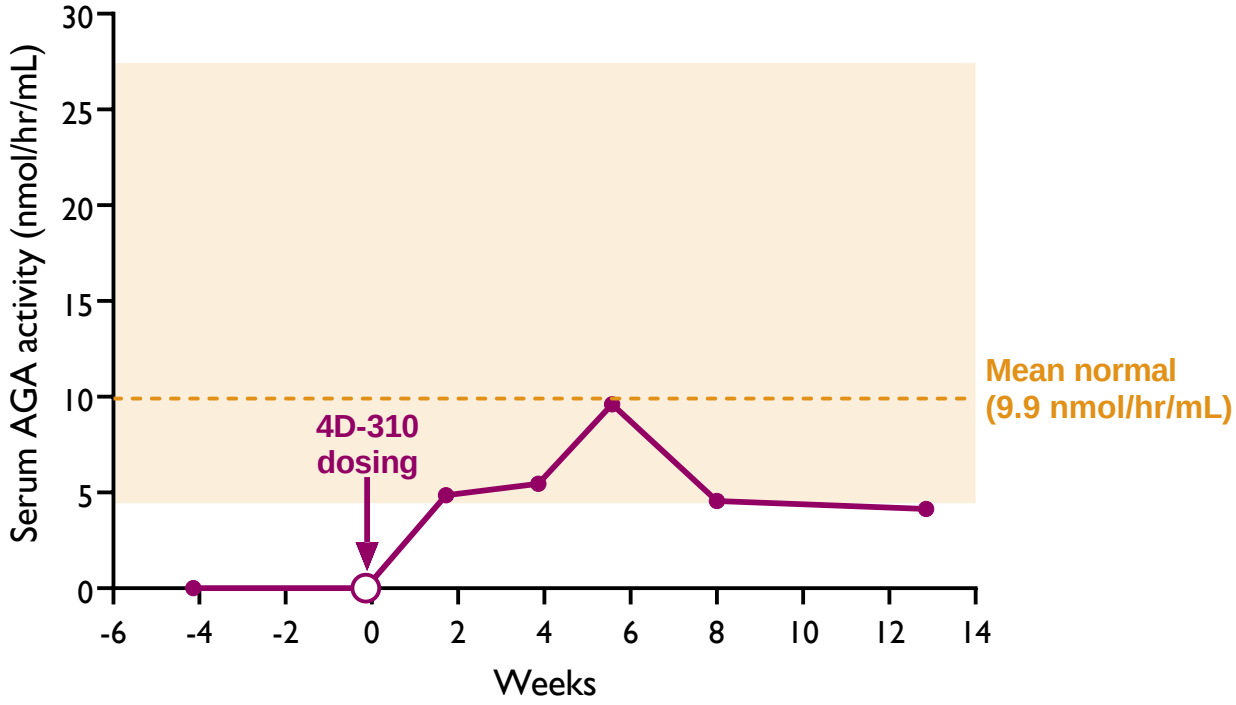
BASELINE CHARACTERISTICS

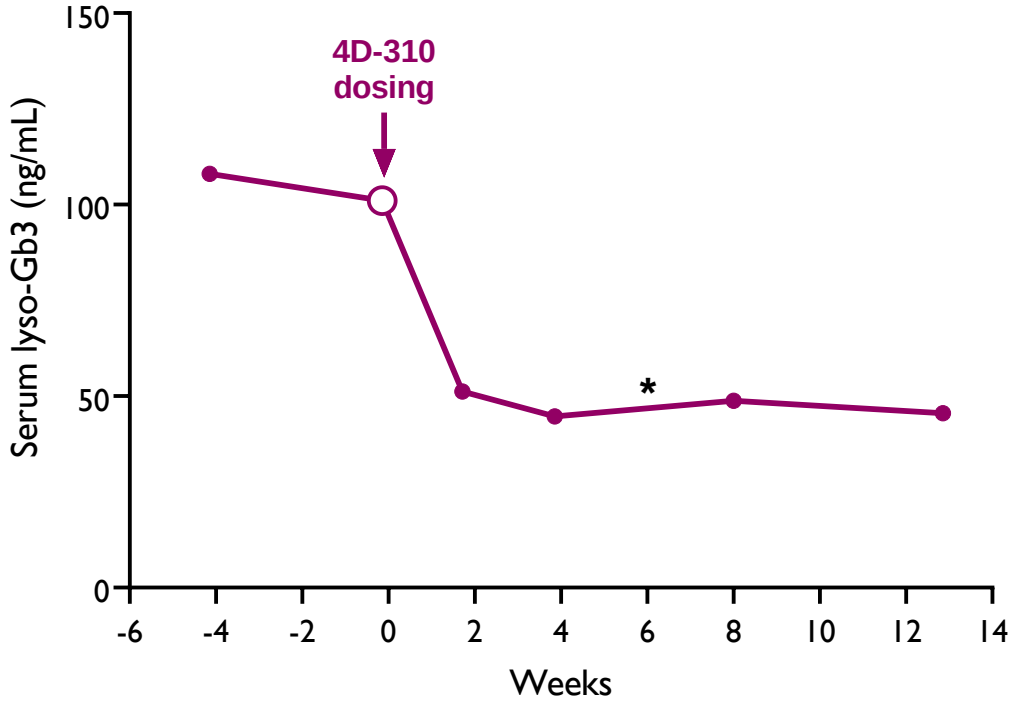
Anti-AGA Ab Status	ERT Status (lyso-Gb3)	ERT Experience
1:13,900	ERT-**ON;** low lyso-Gb3	Yes

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: AGA Activity & Lyso-Gb3

AGA ACTIVITY WITHIN NORMAL RANGE; LYSO-GB3 DECREASED AFTER 4D-310





BASELINE CHARACTERISTICS

Anti-AGA Ab Status	ERT Status (lyso-Gb3)	ERT Experience
1:99,900 (24X mean)	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

Interim Safety & Tolerability Summary

4D-310 ON-GOING PHASE 1/2 CLINICAL TRIAL

- 4D-310 demonstrated a manageable safety profile
- No dose-limiting toxicities
- No 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 aHUS, 2 Pts Without

COMPLEMENT ACTIVATION RELATED LABORATORY VALUES: CTCAE GRADE

	BL	D8	D15	W4	W6	W8	W12	W26
Creatinine								
Patient 1	-	-	-	-	-	-	-	-
Patient 3	-	-*	-	-				
Patient 2	-	3	2	-	-	-	-	
Platelet count								
Patient 1	-	-	-	-	-	-	-	-
Patient 3	-	-	-	-				
Patient 2	-	2	1	-	-	-	-	

- (within normal range)

*Grade 2 proteinuria & Grade 1 LDH elevation, PT/PTT within normal limits

Liver Function Labs: No Clinically Significant Toxicity

LIVER LABORATORY VALUES: CTCAE GRADE

	BL	D8	D15	W4	W6	W8	W12	W26
AST								
Patient 1	-	-	-	-	-	-	-	-
Patient 3	-	-	-	-				
Patient 2	-	-	-	-	-	-	1*	
ALT								
Patient 1	-	-	-	-	-	-	-	-
Patient 3	-	-	-	-				
Patient 2	-	-	-	-	-	-	1*	
Bilirubin								
Patient 1	-	-	-	-	-	1	-	-
Patient 3	-	-	-	-				
Patient 2	-	-	-	-	-	-	-	

- (within normal range)

*Grade 1 ALT, AST subsequently resolved

Summary of Interim Data for 4D-310 Ph 1/2 Clinical Trial

DATA CUT-OFF DATE: 10/12/21

- 4D-310 demonstrated a manageable safety profile and no DLTs
- Clinical activity was observed in all patients at all timepoints
  - Mean **AGA** enzyme activity was within, or significantly above, the normal range in all three patients
  - Serum **lyso-Gb3** substrate decreased significantly in patient with elevated pre-treatment lysoGb3 (entered study OFF-ERT)
  - Serum **lyso-Gb3** substrate remained low following discontinuation of ERT in BOTH patients who entered study ON-ERT

4D-310 Acknowledgements

THANK YOU TO PATIENTS, FAMILIES & CLINICAL TRIAL SITE COLLABORATORS!

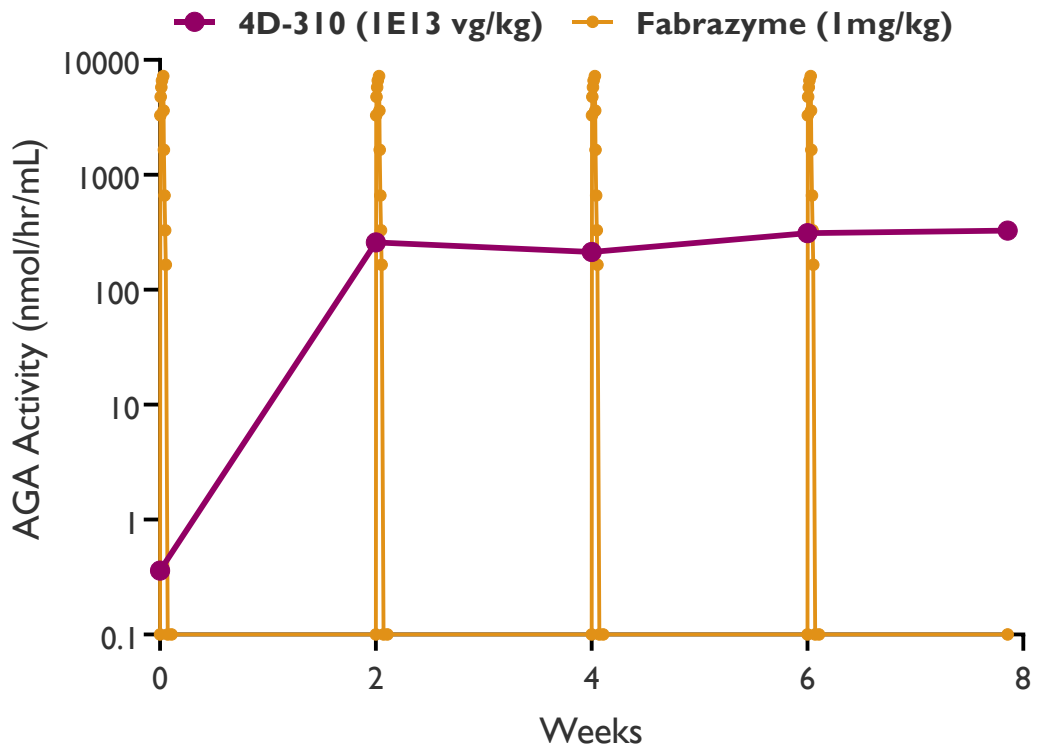
Investigators and Clinical Trial Participants

- Gerard Vockley, MD, PhD
  - Children's Hospital of Pittsburgh, UPMC
- William Wilcox, MD, PhD
  - Emory University
- Ozlem Goker-Alpan, MD
  - Lysosomal & Rare Disorders Research & Treatment Center, Inc
- Nicola Longo, MD, PhD
  - University of Utah

4D-310 AGA Activity: Comparison to ERT & Other Gene Therapy

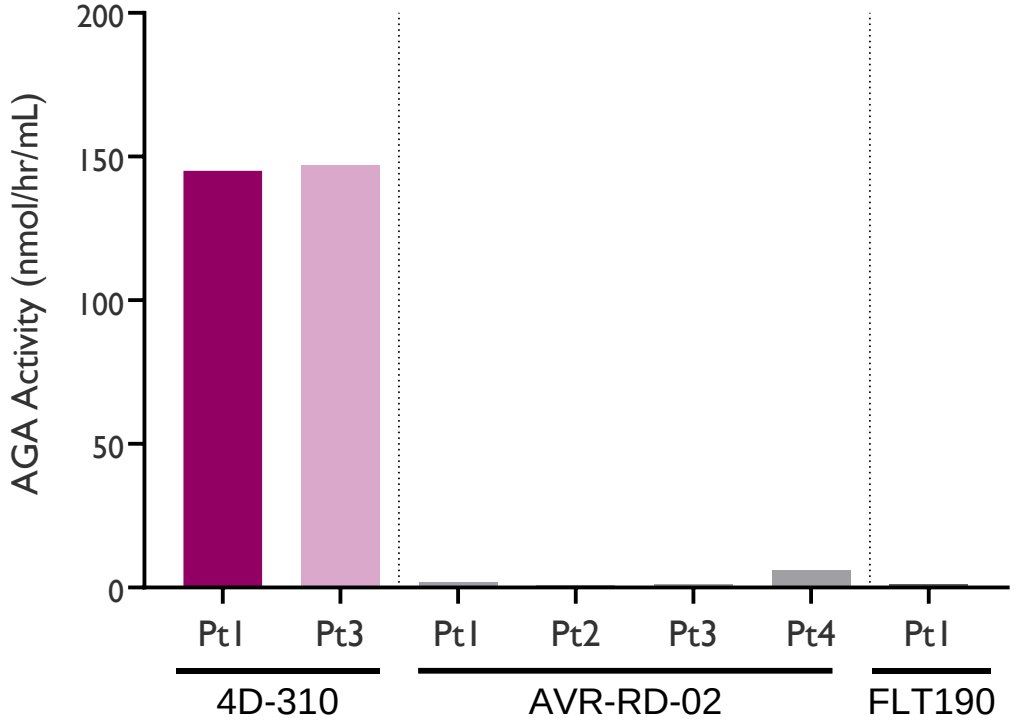
4D-310 AGA ACTIVITY RELATIVE TO STANDARD OF CARE, LENTIVIRAL & CONVENTIONAL AAV GT

AGA Activity
4D-310 vs SOC ERT (Fabrazyme)



- 4D-310: Average of patients 1 & 3
- Fabrazyme: 1mg/kg BW; Nakamura et al. Mol Genet Metab,2020;130:215

AGA Activity
4D-310 vs Other Gene Therapy
(last available follow-up)



- 4D-310: Activity measured in Mayo Clinic Lab; serum AGA reference range: 4.44 – 27.42 nmol/hr/mL.
- AVROBIO: Presentation in World symposium 2021; plasma AGA activity reference range: 5.1 – 9.2 nmol/hr/mL.
- Freeline: Presentation in World symposium 2020

4D-310 Development Program: Next Steps

- Continue enrolling at 1E13 vg/kg dose level: Expansion cohort US Study
  - Broad population
  - Classic & Late-Onset patients
  - AGA Ab (+) & (-)
  - Exclusion criteria change: AGA Ab titer >1:25,000 (est exclude ~5% of all patients)
  - ERT (+) & (-)

- Initiate Phase 1/2 Asia-Pacific clinical trial (open Taiwan IND), including assessments of transgene delivery via cardiac biopsy

4D-110 Phase 1/2 Clinical Trial: Data Update

Clinical Activity: Preservation of RPE cells and Photoreceptors

BASELINE TO LAST VISIT; N=2 EVALUABLE & WITH AT LEAST 12 MONTHS FOLLOW-UP; 3E11 VG/EYE

		Fundus Autofluorescence (FAF) Area % Change from Baseline (Absolute Change)		**Ellipsoid Zone Area (EZA)** % Change from Baseline (Absolute Change)	
Patient	Last Assessment	**Treated Eye**	Untreated Eye	**Treated Eye**	Untreated Eye
Cohort 1 (3×10^{11} vg/eye)					
1	Month 12	**-7.3%** (-0.26)	**-9.5%** (-0.38)	**-8.9%** (-0.7)	**-10%** (-0.47)
2	Month 10+	**-4.4%** (-1.93)	**-6.1%** (-2.73)	**-9.5%** (-3.13)	**-12%** (-4.19)

* Rate of progression normalized for same # months
\+ Patient 2 latest evaluable scans 10 months

Ocular Inflammation: SUN Score

ANTERIOR CHAMBER CELL*

	BL	D14	M1	M2	M3	M6	M9	M12
Cohort 1 (3×10^{11} vg/eye)								
Patient 1	0	0	0	0.5	0.5	0	0.5	0.5
Patient 2	0	0	2	0.5	0	0	1	0.5
Patient 3	0	0	0	0	0	1	0	
Cohort 2 (1×10^{12} vg/eye)								
Patient 4	0	0	0	0	0	0		
Patient 5	0	0	0.5	0.5	0	0.5		
Patient 6	0	0.5	2	0.5	1	0		

*Standardization of Uveitis (SUN) Nomenclature Grading Scheme [SUN Working Group 2005 (Jabs et al., 2005)]

Ocular Inflammation: NEI Score

VITREOUS CELL*

	BL	D14	M1	M2	M3	M6	M9	M12
Cohort 1 (3×10^{11} vg/eye)								
Patient 1	0	0	0	0.5	0.5	0	0.5	0.5
Patient 2	0	0	0	1	0.5	0.5	0.5	0
Patient 3	0	0	0.5	0.5	0.5	1	0.5	
Cohort 2 (1×10^{12} vg/eye)								
Patient 4	0	0	0	0	0	0		
Patient 5	0	0	0	0.5	0	0.5		
Patient 6	0	0	0.5	0.5	0.5	1		

*National Institutes of Health Grading System for Vitreous Cells (Mahendradas, Khanna, Kawali, & Shetty, 2014)

Key Takeaways for 4D-110 Clinical Data

TOLERABILITY @3E11 VG/EYE ASSOCIATED WITH CLINICAL ACTIVITY

- 3E11 vg/eye dose (Cohort 1):
  - Well-tolerated & no DLT or SAE
  - Clinical activity vs control eyes (FAF Area)
- 1E12 vg/eye dose (Cohort 2):
  - Pigment dispersion syndrome (inc iris transillumination; n=3): Grade 3 - onset 7.5-9 months
  - Consistent with REP1 transgene product over-expression (no association with inflammation)
- Cohort 1 Expansion at 3E11 vg/eye dose

4DMT Expected Near-Term Milestones

COMMITMENT TO RELENTLESS EXECUTION

4D-150	**1Q22** - PHASE 1/2 FIRST PATIENT DOSED
4D-125	PHASE 1/2 ENROLLMENT: DOSE-EXPANSION
4D-110	PHASE 1/2 ENROLLMENT: DOSE-EXPANSION

4D-310 **2022** - PHASE 1/2 ADDITIONAL CLINICAL DATA

4D-710 **1H22** - PHASE 1/2 FIRST PATIENT DOSED

THANK YOU

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