



4DMT

A Targeted AAV Gene Therapy Product Candidate, 4D-310, for the Treatment of Fabry Disease: Intravenous Biodistribution, Transgene Expression & Safety in Non-Human Primates

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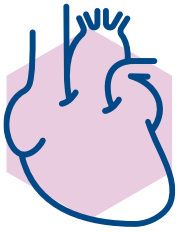
This Presentation discusses our product candidates that are under preclinical study and in clinical trials, and which have not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of our product candidates for the therapeutic use for which they are being studied.

This Presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Presenter Disclosures

- The presenter is Vice President of Translational Medicine and a full-time employee of 4D Molecular Therapeutics, Inc.

4D-310: Dual Mechanism-of-Action Gene Therapy for Fabry Disease



HIGH UNMET MEDICAL NEED

- **Monogenic X-linked (*GLA*)**
- **Heart disease:** main cause of death
- **ERT therapies:** lack therapeutic concentrations



EPIDEMIOLOGY: US & EU-5

- ~ **19,000** total addressable patients
- **50,000 - 70,000** newborn screening



PRODUCT DESIGN

- **Vector:** C102
- **Transgene:** *GLA*
- **Promoter:** Ubiquitous

DIFFERENTIATION

Dual MOA - Whole Organ Correction

One-time administration

Efficacy potential despite prior ERT & AGA Ab

Classic, Non-Classic & Female Patient Populations

STATUS:

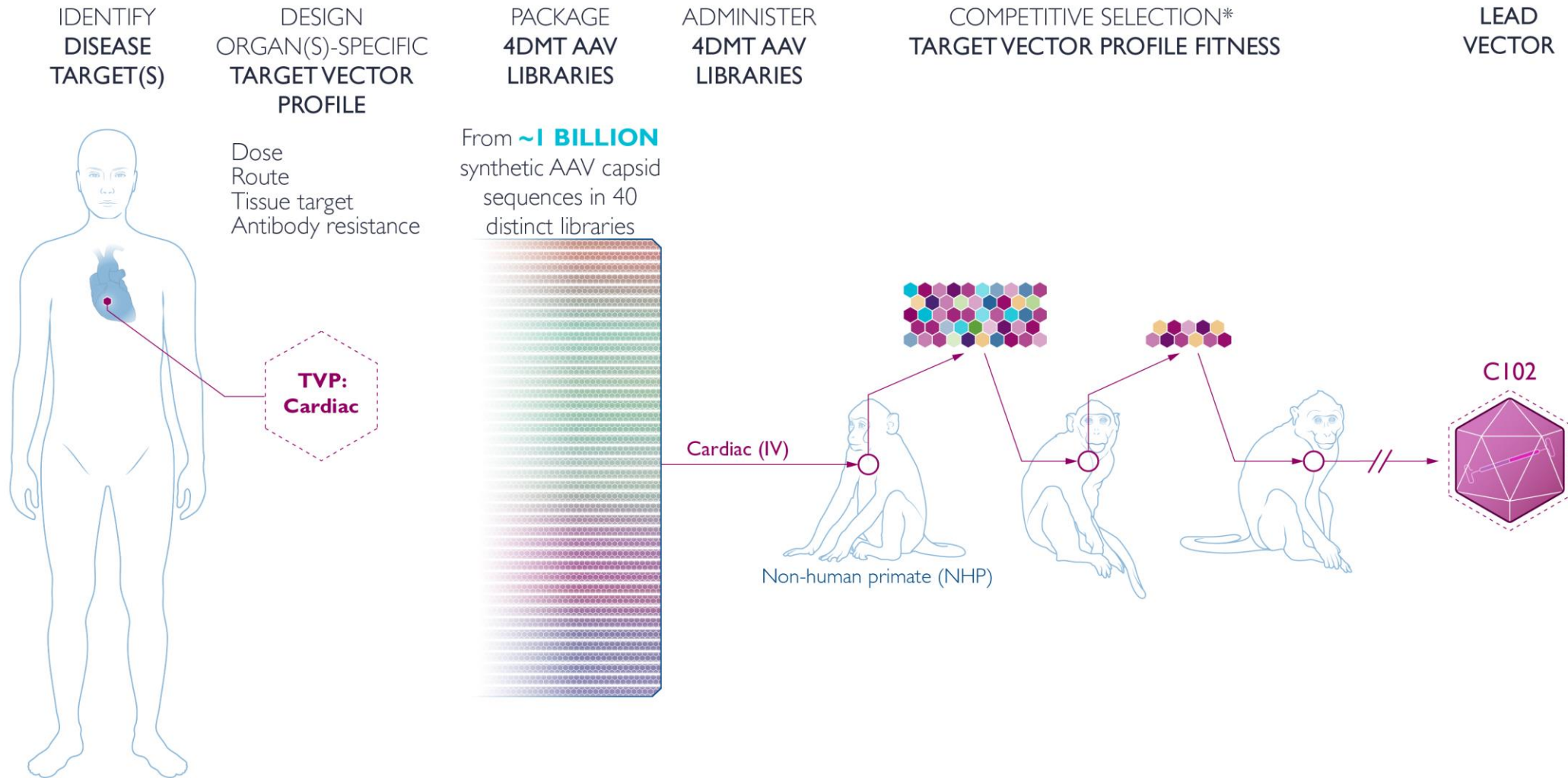
Ongoing Phase 1/2 Clinical Trial

EXPECTED MILESTONE:

Initial Clinical Data in 2H21

Invention of C102 by Therapeutic Vector Evolution

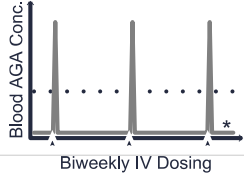
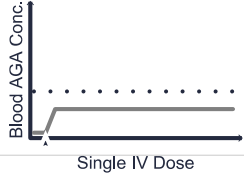
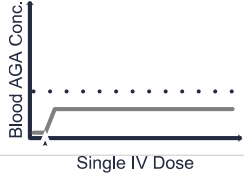
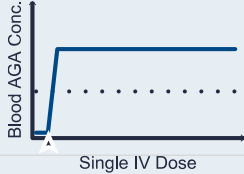
TARGET VECTOR PROFILE (TVP): ENHANCED LOW DOSE DELIVERY & TRANSDUCTION WITHIN HEART TISSUE



*Capsid library placed under varying selective pressures // Actual number of selection rounds varies by target

4D-310 Therapeutic Objectives in Fabry Disease

DESIGNED FOR DUAL MECHANISM-OF-ACTION

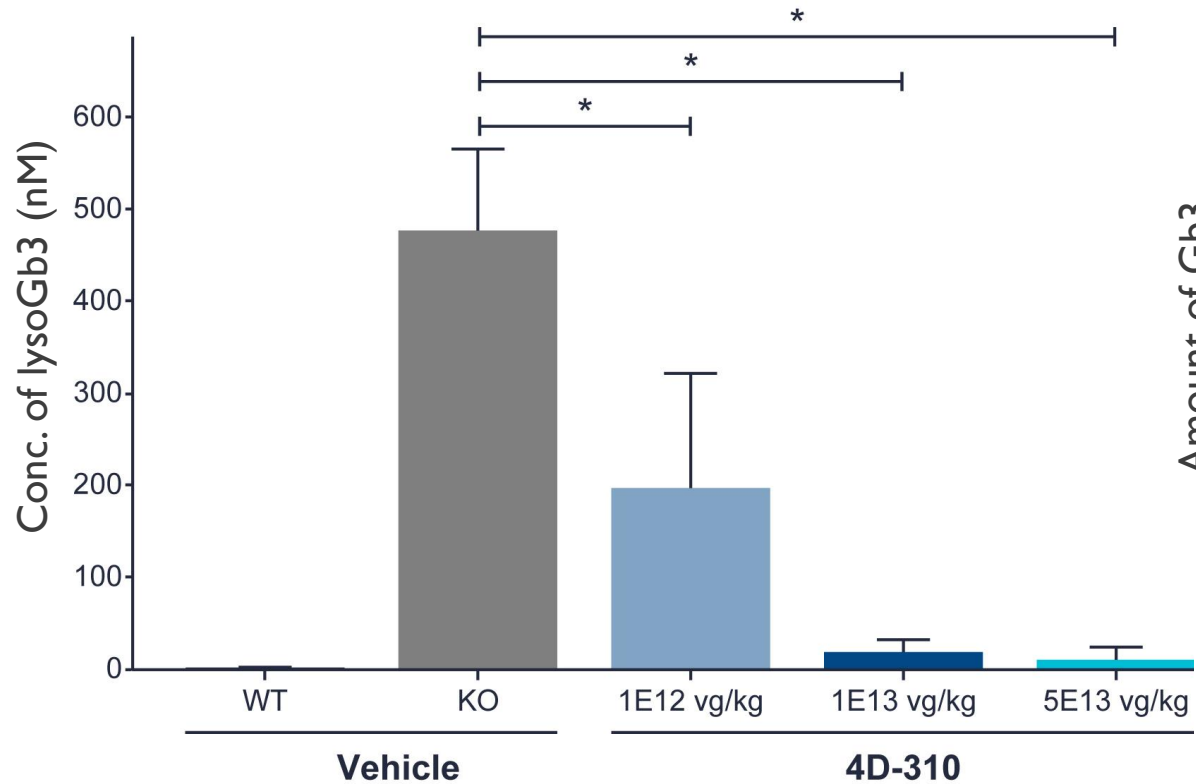
MOA	Product Design	ERT	Gene Therapy		
		AGA Enzyme Infusions	Patient-derived Stem Cells	AAV-mediated Liver-directed	4D-310
AGA Delivery Through the Bloodstream	Pharmacokinetics				
	Cross-correction endothelial cells	+	+	+	+
	Single dose administration	-	+	+	+
	Stable sustained concentration of AGA enzyme activity in blood	-	+	+	+
	AGA production & secretion from the liver	-	-	+	+
	No required chemotherapy—bone marrow ablation	n.a.	-	+	+
AGA Production in Target Cells	Heart	-	-	-	+
	Kidney	-	-	-	+
	Blood vessels	-	-	-	+
Avoid AGA Neutralization	Intracellular production	-	-	-	+

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

4D-310 Efficacy in Fabry Knockout Mice

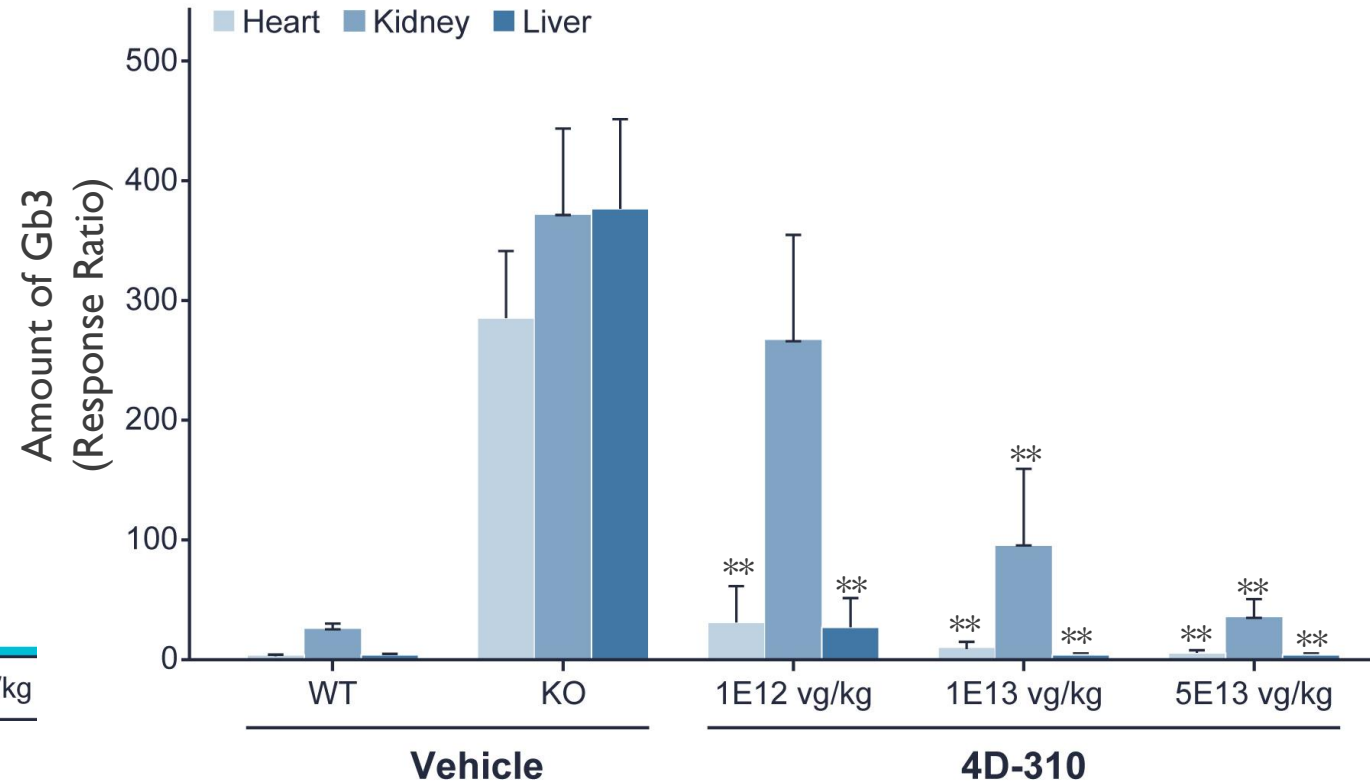
DOSE-DEPENDENT SUBSTRATE REDUCTION; NO 4D-310 RELATED TOXICITY OBSERVED

Plasma LysoGb3 Substrate Reduction



N = 15 mice per group
* p < 0.0001

Tissue Gb3 Substrate Reduction



N = 12 mice per group
** p < 0.01 compared with KO Vehicle

4D-310 NHP Dose-Ranging Study Design

GROUP	N	TREATMENT	ROUTE	DOSE (VG/KG)	IN-LIFE	ENDPOINTS
1	1	Vehicle	IV	N/A	8 wks	<ul style="list-style-type: none"> ▪ Clinical evaluation ▪ Clinical chemistry ▪ Vector distribution & expression ▪ AGA activity in plasma & tissues
2	3	4D-310	IV	3E12	8 wks	
3	3	4D-310	IV	1E13	8 wks	
4	3	4D-310	IV	5E13	8 wks	

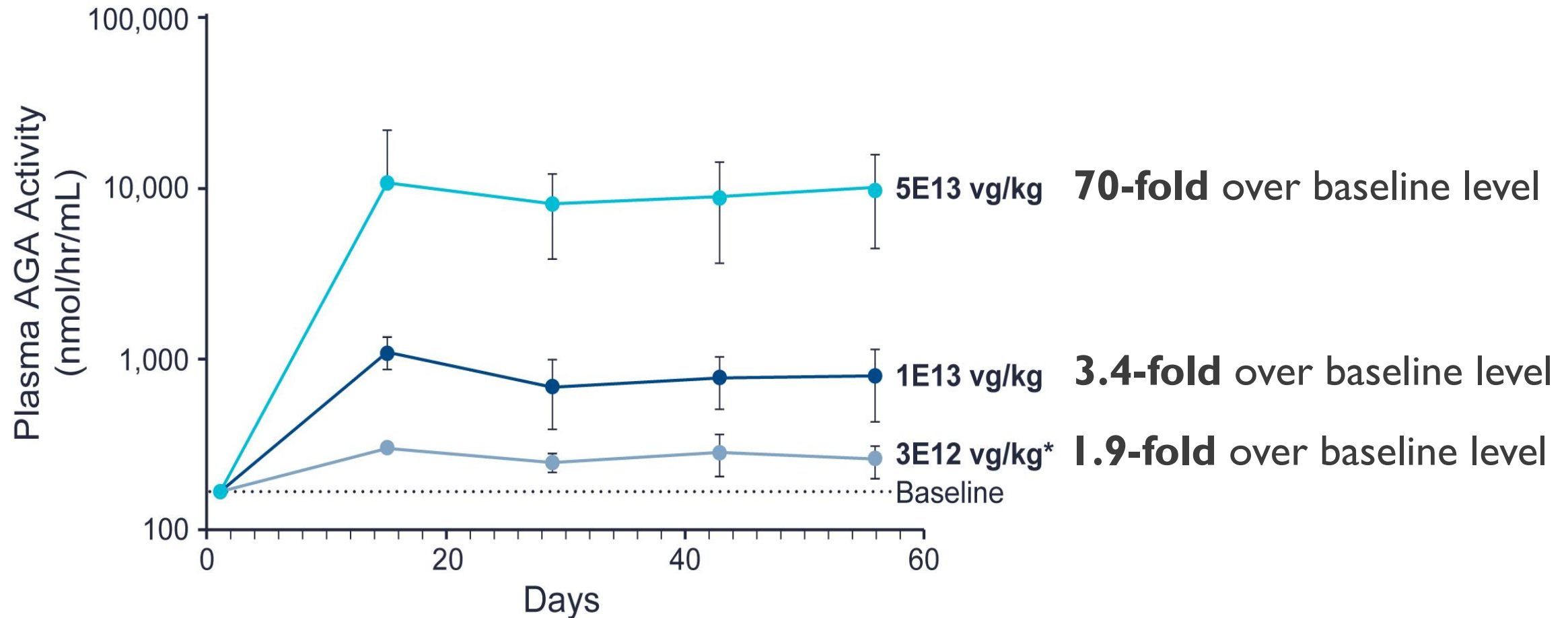
Summary of 4D-310 Key Safety Endpoints in NHPs

NO 4D-310 RELATED TOXICITY OBSERVED

PARAMETER	KEY OBSERVATIONS
Body Weight	Normal over time in all dose groups
Liver Enzymes	3E12 and 1E13 dose groups: no change 5E13 dose group: minimal transient increase in ALT activity on Day 7 (fully resolved)
Total Bilirubin	No effect
Creatine Kinase	Minimal transient increase in CK activity on Day 7 (fully resolved) (attributed to intramuscular steroid injection)
Hematology	No effect

4D-310 Pharmacodynamics in NHPs

DOSE-DEPENDENT STABLE AGA ACTIVITY IN PLASMA



*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 Biodistribution in NHPs

SUCCESSFUL DELIVERY TO & TRANSDUCTION OF KEY TISSUES TO TREAT FABRY DISEASE

GROUP	HEART (LV)	KIDNEYS	LIVER	CAROTID
Genomes (qPCR)	18/18 (100%)	18/18 (100%)	18/18 (100%)	8/8 (100%)
mRNA (RT-qPCR)	18/18 (100%)	18/18 (100%)	18/18 (100%)	6/6 (100%)

- In all NHPs administered 4D-310: Delivery (genomes) & transduction (mRNA) were consistently measured throughout organs important to the management of Fabry Disease

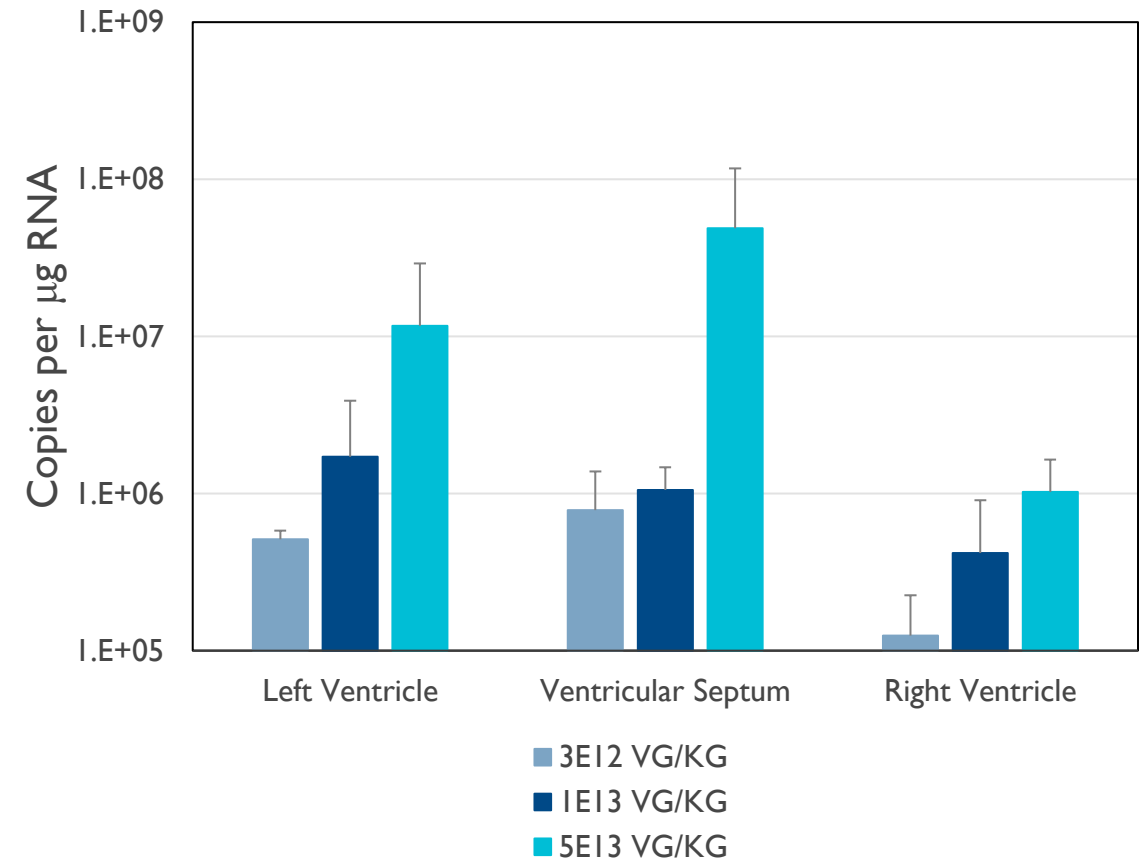
4D-310 Biodistribution in NHPs

TRANSGENE RNA EXPRESSION SHOWN IN HEART AT ALL DOSE LEVELS

Frequency of Expression in Heart Samples

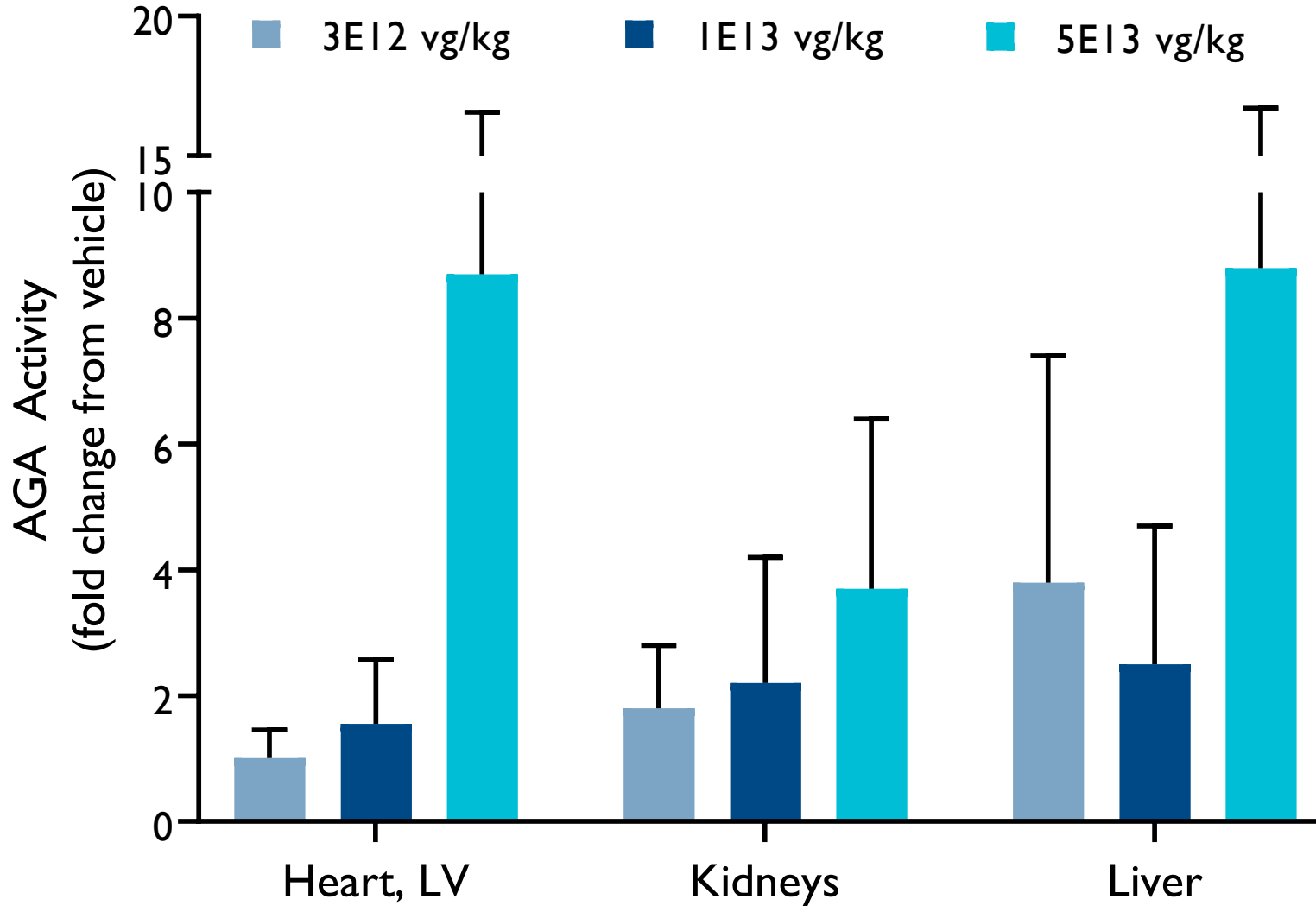
GROUP	3E12 VG/KG	1E13 VG/KG	5E13 VG/KG
Left Ventricle	3/3 (100%)	3/3 (100%)	3/3 (100%)
Ventricular Septum	3/3 (100%)	3/3 (100%)	3/3 (100%)
Right Ventricle	3/3 (100%)	3/3 (100%)	3/3 (100%)

Dose-Related Expression in Heart Samples



4D-310 Pharmacology in NHPs

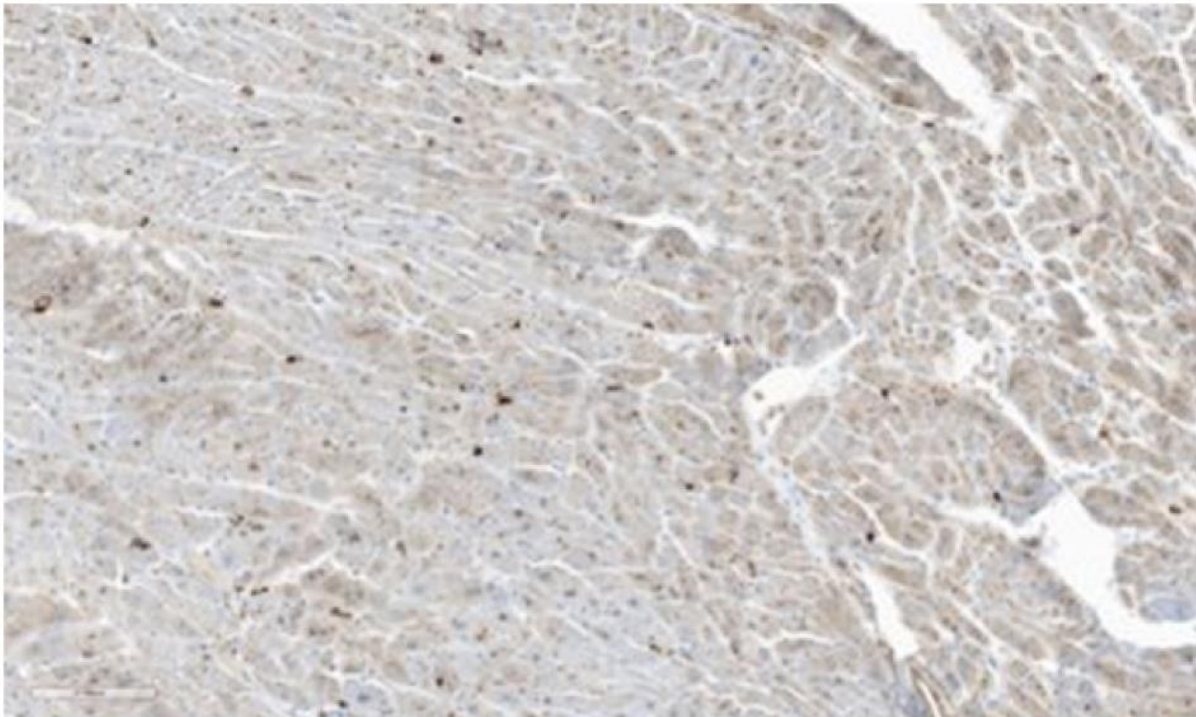
AGA ACTIVITY IN KEY FABRY TISSUES



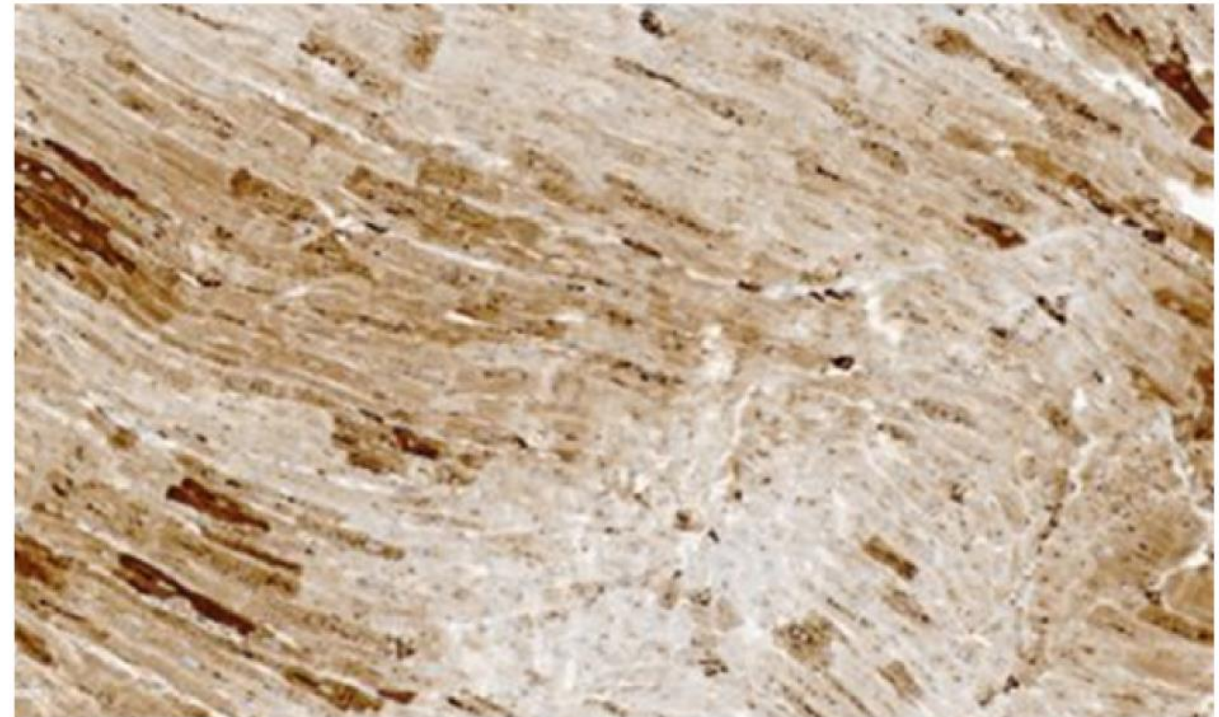
4D-310 Biodistribution in NHPs

REPRESENTATIVE IMMUNOHISTOCHEMISTRY OF AGA IN HEART LEFT VENTRICLE

Vehicle



4D-310 5E13 vg/kg



20X magnification

Summary and Conclusions

- C102 vector invented for low dose IV delivery to the heart, cardiomyocyte transduction, and resistance to neutralizing antibodies
- 4D-310 designed for unique dual mechanism-of-action: high AGA blood levels, high AGA expression in heart
- 4D-310 showed dose-dependent clearance of substrate in all key tissues in Fabry knockout mouse model
- Dual MOA confirmed in NHPs:
 - Dose-related 4D-310 delivery and AGA expression throughout the heart
 - 4D-310 produced high-level and dose-dependent plasma AGA activity
 - No 4D-310 related adverse effects observed
- 4D-310 is currently being tested in a Phase I/2 clinical trial in patients with Fabry Disease (NCT04519749)

Acknowledgements

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Thank you!

QUESTIONS?

