4DMT

Harnessing the Power of Directed Evolution for Targeted, Next-Generation Genetic Medicines

Corporate Presentation | May 2024

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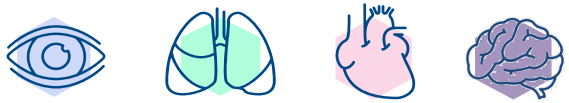
Leading Clinical Stage Next Generation AAV Company

Mission: *Become a Fully Integrated Biopharma Company Boldly Innovating to Unlock the Full Potential of Genetic Medicines for Millions of Patients*

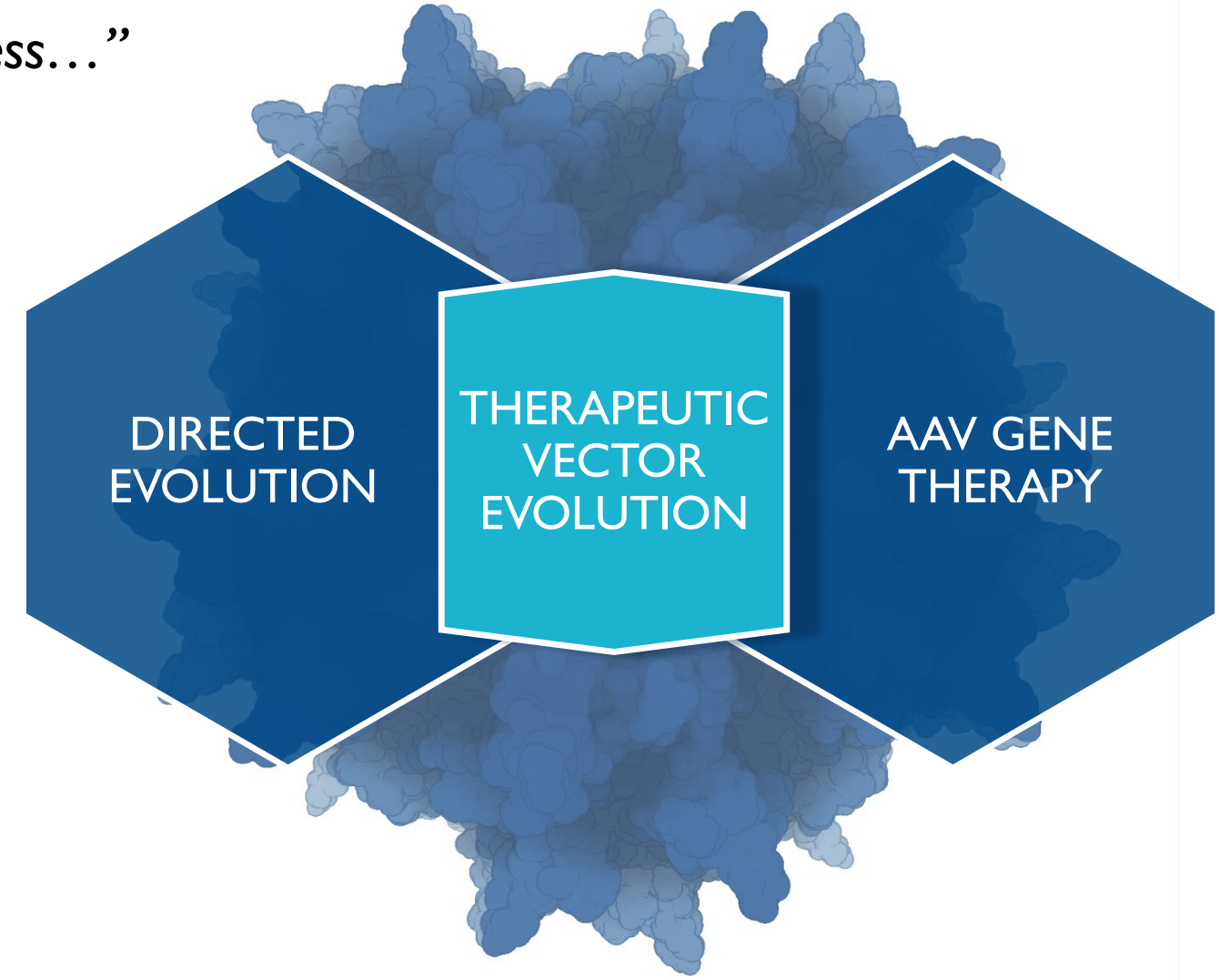
PLATFORM	**DIRECTED EVOLUTION** Nobel Prize-Winning Technology	**~1 BILLION** Proprietary Capsid Sequences	**MODULAR** Customized & Evolved Vectors + Optimized Payloads
PRODUCT ENGINE	**CLINICAL PROOF-OF-CONCEPT**	**4 THERAPEUTIC AREAS** 	**3 ROUTES OF ADMIN** Intravitreal Aerosol Intravenous
PIPELINE		**5 CLINICAL CANDIDATES** **7 PATIENT POPULATIONS** 4 Large Market Opportunities **2 IND CANDIDATES**	**FDA RMAT & EMA PRIME DESIGNATION** **4D-150 for Wet AMD**
CAPABILITIES	**IN-HOUSE** GMP Manufacturing	**NEXT GENERATION** Vector Discovery & Payload Design	**STRONG BALANCE SHEET** **$589M** cash as of Q1 2024 Runway through H1 2027

Platform Solution: Therapeutic Vector Evolution

Innovation Through Nobel Prize-Winning Technology for Biologics

"…the most powerful biological design process…"

– Frances Arnold,
*2018 Nobel Prize in Chemistry**



*Dr. Arnold and the other investigators awarded the Nobel Prize have no affiliation with 4DMT.

Successes & Limitations of Conventional AAV

Opportunity For Targeted Genetic Medicine Vectors & Products

SUCCESSES

zolgensma®

LUXTURNA®

avexis

Spark THERAPEUTICS

Elevidys

SAREPTA THERAPEUTICS

HEMGENIX®

uniQure

ROCTAVIAN

BIOMARIN®

LIMITATIONS

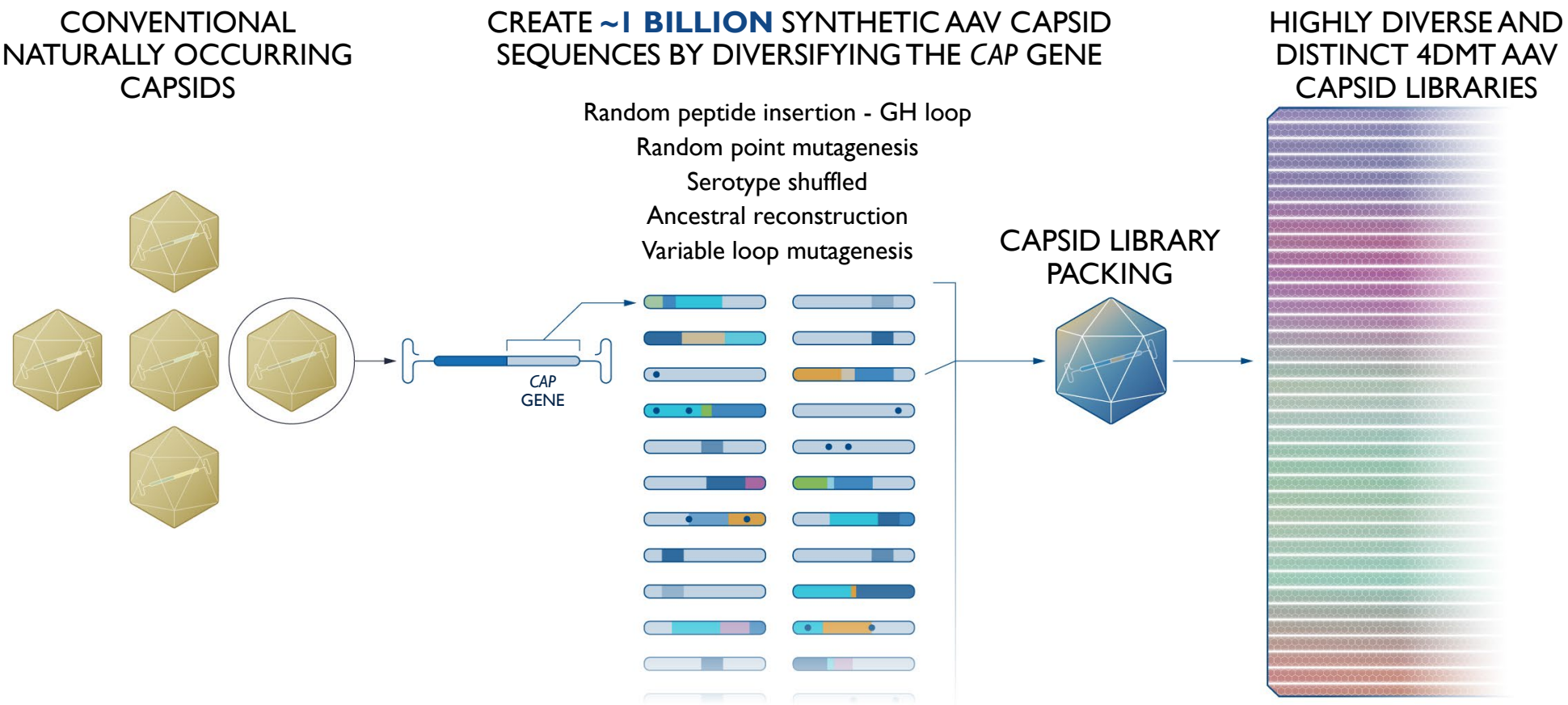
- Limited Delivery
- Limited Transduction
- Increased Inflammation and Toxicity
- Vulnerability to Neutralizing Antibodies

Narrow Focus on Niche Diseases

OPPORTUNITY:
UNLOCK THE FULL POTENTIAL OF GENETIC MEDICINES BY HARNESSING THE POWER OF DIRECTED EVOLUTION

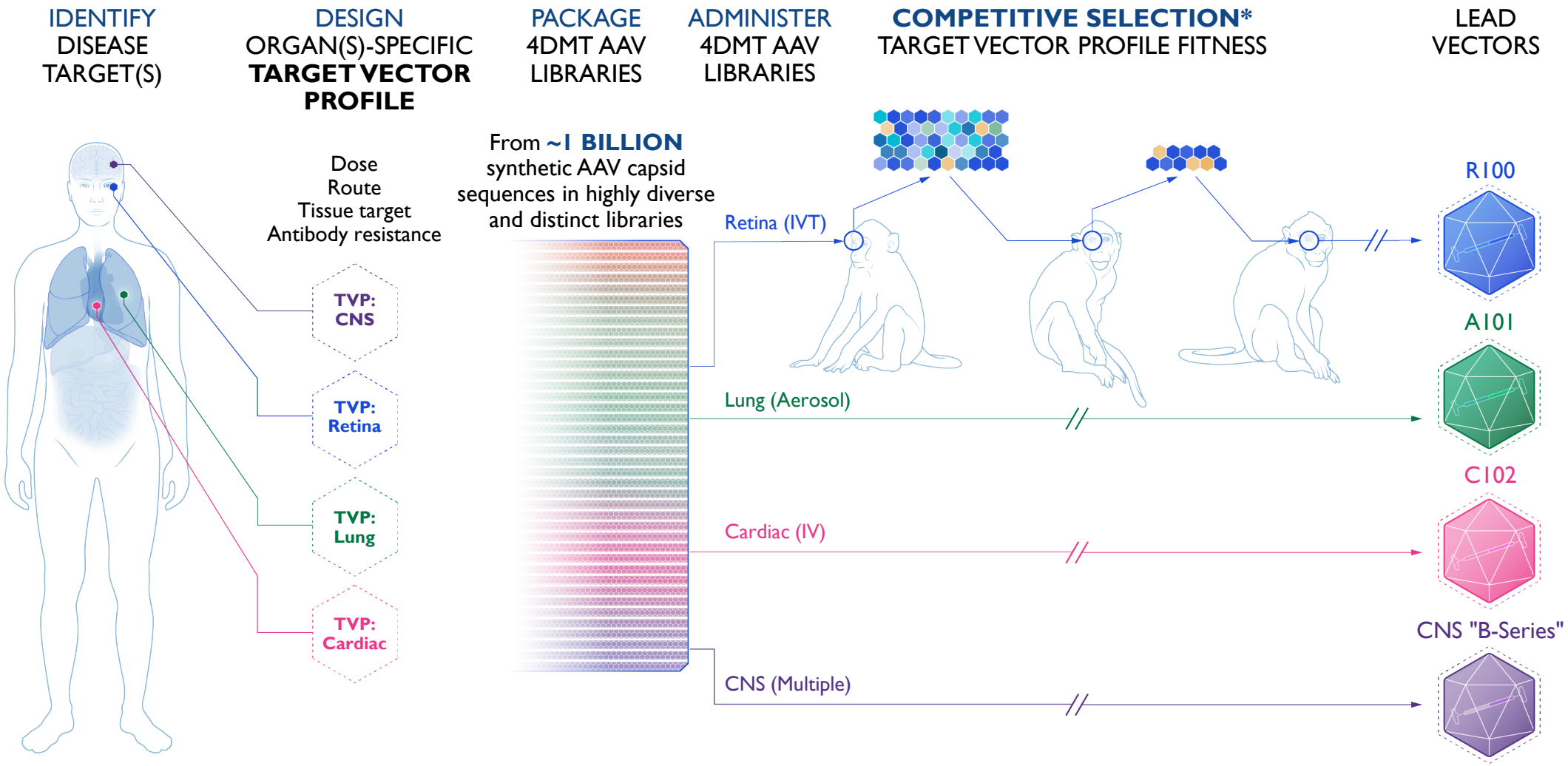
Platform Solution: ~1 Billion Synthetic Capsid Sequences

Step 1: Create Massive Diversity in Highly Diverse and Distinct Libraries



Platform Solution: Target Vector Profile Fitness Competition

Steps 2 & 3: Therapeutic Vector Evolution



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

Unlocking the Full Potential of Genetic Medicines: Multiple Large Market Opportunities

VECTOR / DELIVERY	PRODUCT CANDIDATE	INDICATION	ESTIMATED PREVALENCE	RESEARCH CANDIDATE	IND-ENABLING	PHASE 1/2	PHASE 3	PRODUCT RIGHTS
OPHTHALMOLOGY **R100** Intravitreal	4D-150	Wet AMD	~3M U.S./EUMM					4DMT
		DME	~5M U.S./EUMM					
	4D-125	XLRP	~24K U.S./EUMM					4DMT
	4D-110	Choroideremia	~13K U.S./EUMM					4DMT
	4D-175	Geographic Atrophy	~2.5M U.S./EUMM					4DMT
	Undisc. *Vector licensed to Astellas*	Undisclosed Rare Disease	*Undisc.*					astellas
PULMONOLOGY **A101** Aerosol	4D-710	CF Lung Disease (mod. ineligible/intolerant)	~15K WW					4DMT
		CF Lung Disease (combo w/ mods)	~90K WW					
	4D-725	A1ATD Lung Disease	~200K U.S./EUMM					4DMT
CARDIOLOGY **C102** IV	4D-310*	Fabry Disease Cardiomyopathy	~50-70K U.S./EUMM					4DMT
CNS **B SERIES** Multiple	Unnamed *Led by Arbor*	Amyotrophic Lateral Sclerosis	~79k U.S./EU/UK					arbor biotech 50/50 WW

*Currently on clinical hold.

Large Market Ophthalmology

Modular Vector: R100

- **4D-150:** Wet AMD & DME
- **4D-175:** Geographic Atrophy

Wet AMD is the Largest Retinal Disease Market Opportunity

Large & Growing Worldwide Retinal Disease Market

>$18B[1]
Retinal Disease Market
by **2028**

>$13.5B[3]
Branded Anti-VEGF Sales
in **2022**

>64M
Eylea Injections
administered worldwide since launch[5]

Wet AMD Prevalence in Major Markets in Next 5 Years: >4 million[1,2]

Estimated U.S. incidence:
>200k new patients
per year[4]

x2

Up to 42% of wet AMD patients may develop bilateral disease[6]

1. Market Scope Retinal Market Report, 2023 2. Clarivate report (2028 estimates). 3. Company reports. Revenue across all indications. 4. Maguire et al. Issue Brief 2012; 17(8) 5. Regeneron Eylea website, across all indications. 6. Rasmussen, A. et al. Eye 2017; 31: 978-80.

Significant Need to Overcome Limitations of Standard of Care Anti-VEGF Therapeutic Regimens for Wet AMD

1

~80% of physicians cite therapeutic **durability** as the greatest unmet need [1]

Leads to chronic undertreatment

2

Oscillating peak-trough anti-VEGF concentrations between injections can lead to **variability in CST**

Leads to CST variability associated with vision loss, fibrosis & geographic atrophy[2,3]

3

Treatment with VEGF-A inhibitors results in **increased VEGF-C levels in the eye**[4]

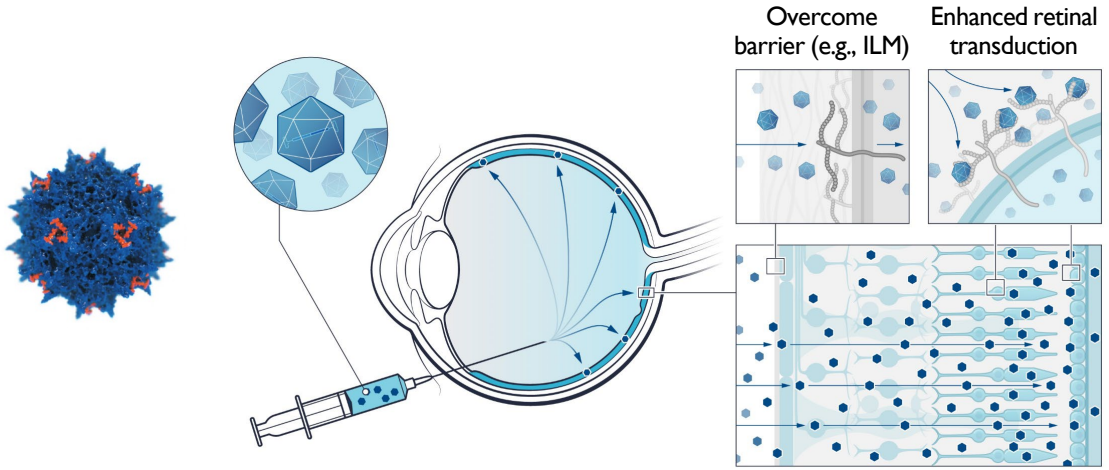
Upregulation of VEGF-C may contribute to treatment resistance[4–6]

All can contribute to vision loss over time while on current standard of care

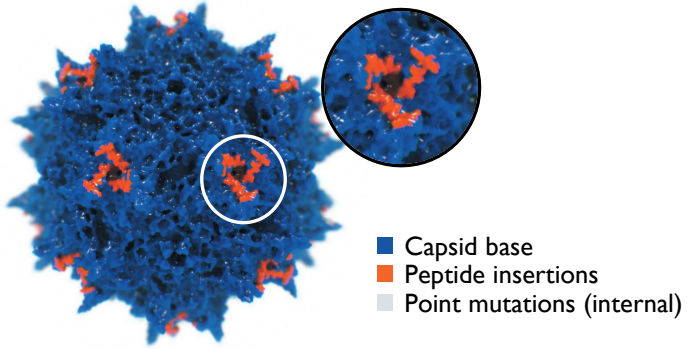
1. 2023 ASRS PAT survey. 2. Guo et al. *Ophthal Res* 2023; 66:406-12. 3. Evans et al. *JAMA Ophtalmol* 2020;138:1043-51. 4. Cabral et al. *Ophthalmol Retina* 2018;2:31-7. 5. Cao et al. *Circ Res* 2004;94:664-70. 6. Pongsachareonnont et al. *Clin Ophthalmol*. 2018;12:1877-85.
CRT, central retinal thickness.

4D-150 Designed to Overcome Limitations of Current Standard of Care with the R100 Vector & Dual Transgene Payload Targeting 4 VEGF Family Members

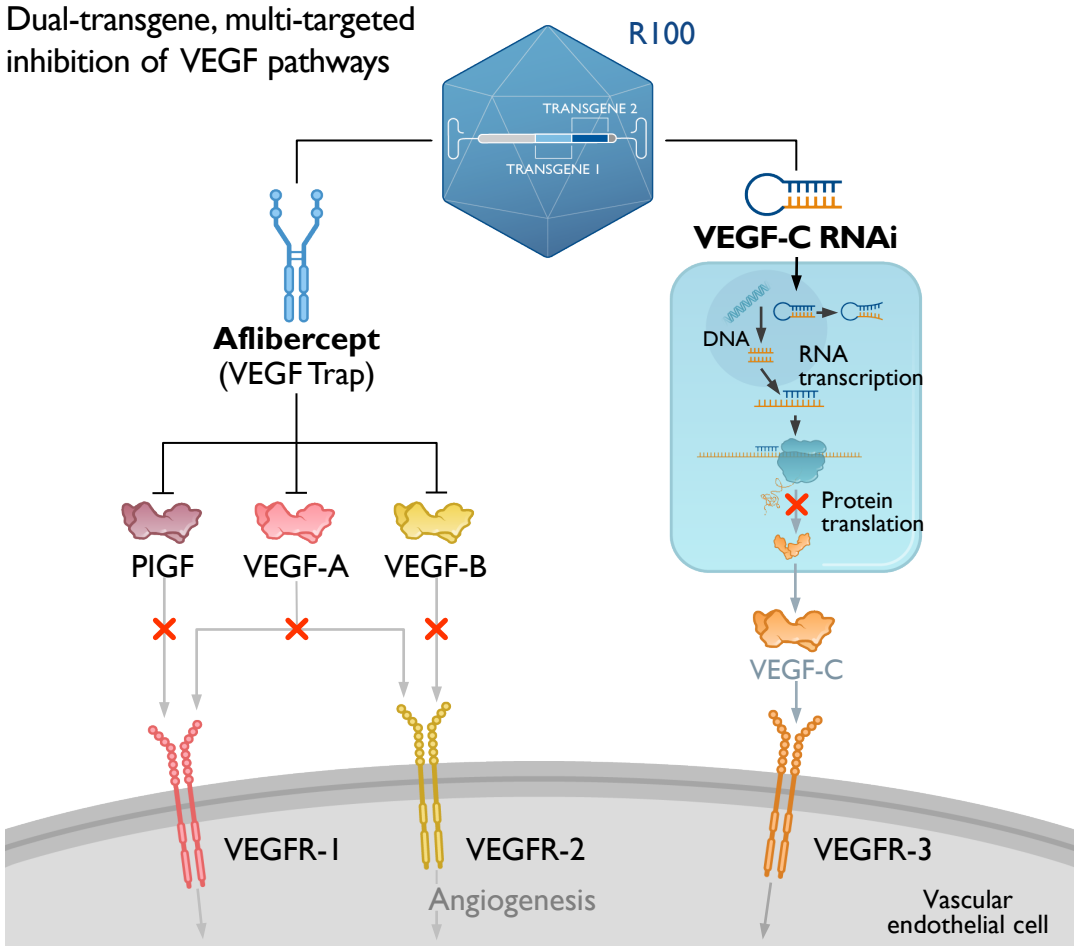
R100



R100 Capsid

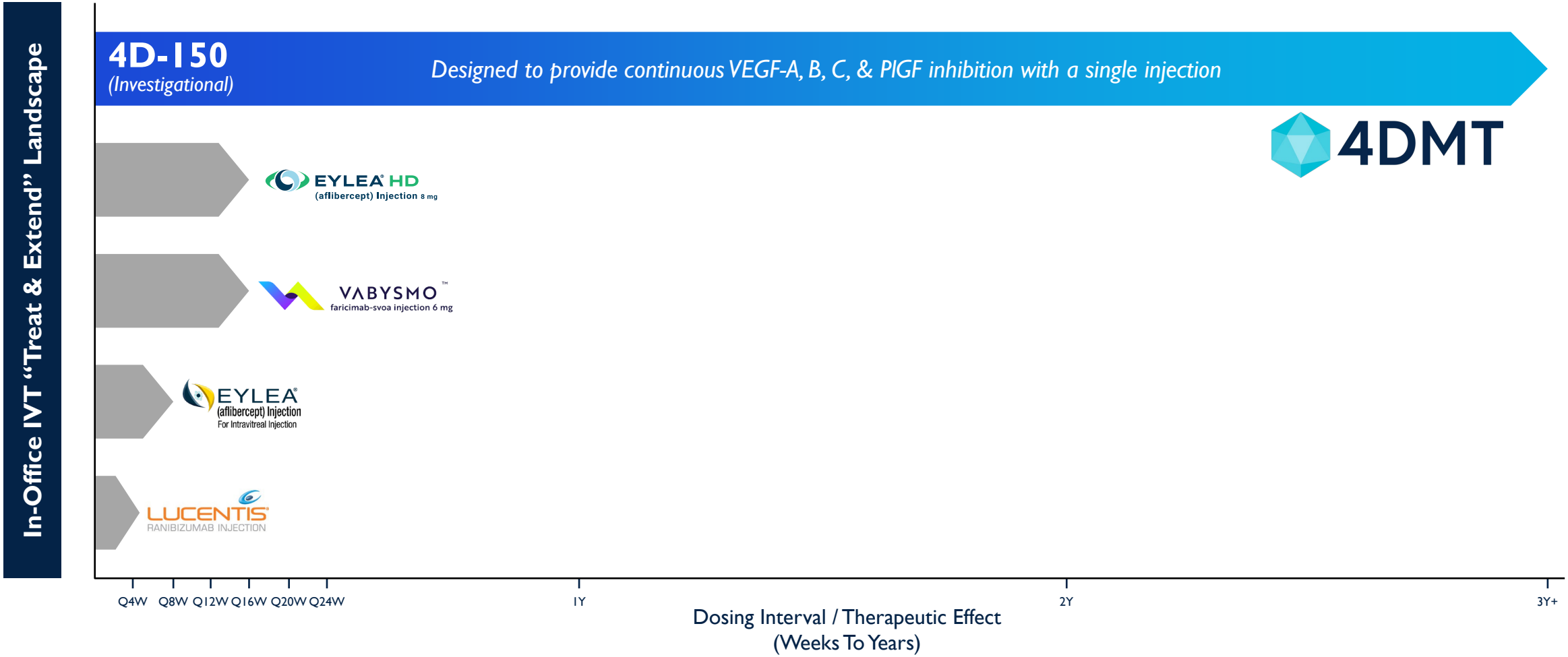


4D-150



Abbreviations: ILM, inner limiting membrane; NHP, nonhuman primate; RPE, retinal pigment epithelium.

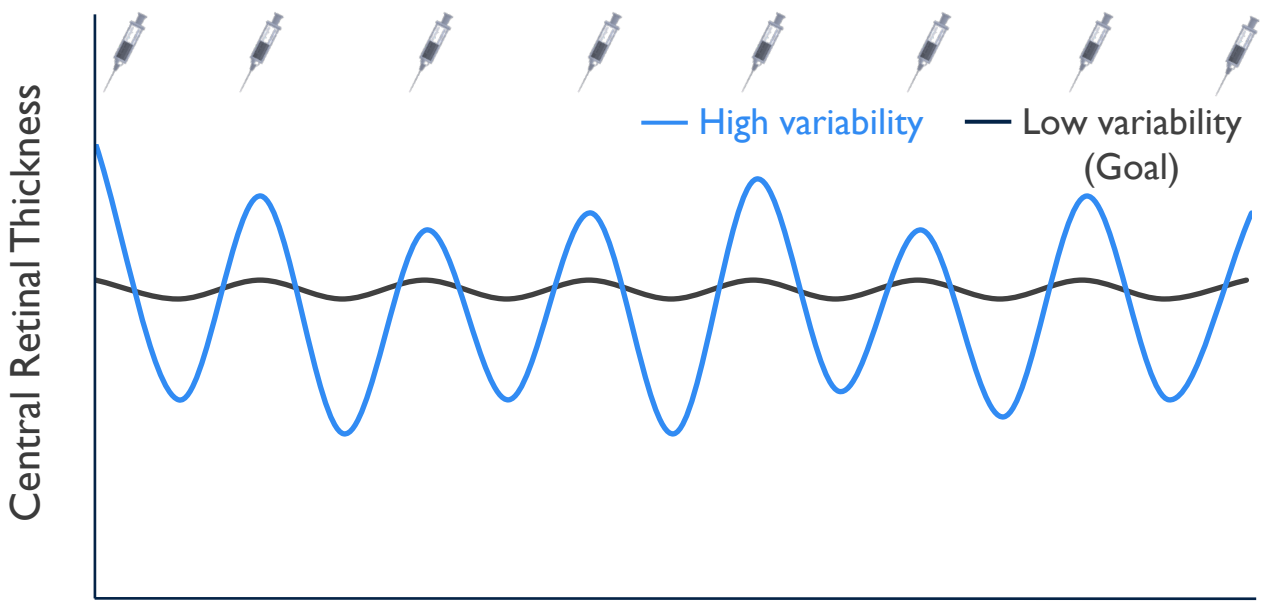
4D-150 Solution: Multi-Year Durability with a Single IVT Injection



FDA labeling.

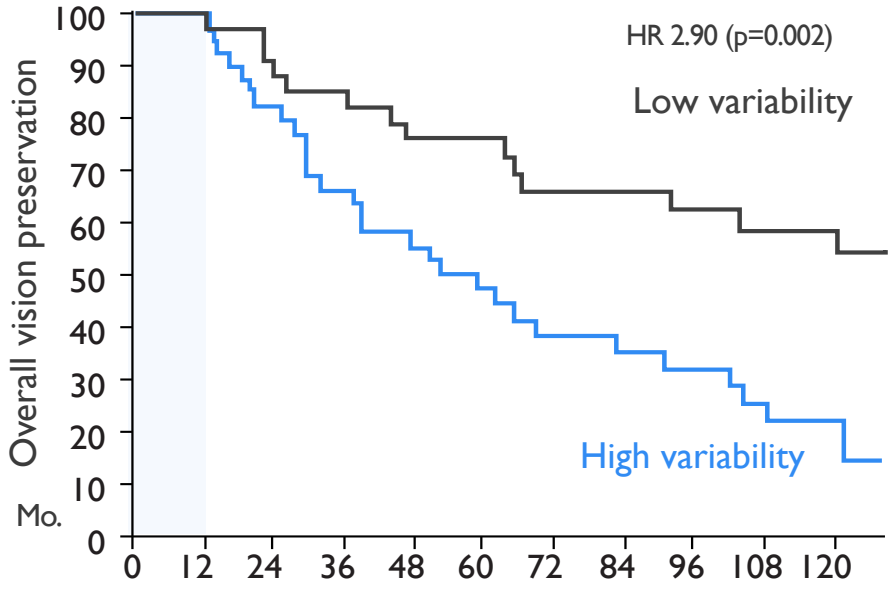
4D-150 Solution: Continuous Retinal Expression of Anti-VEGF to Reduce Retinal Anatomy Variability

Oscillating Peak-Trough Anti-VEGF Concentrations Can Lead to Variability in CST



Illustrative anti-VEGF treatment response

Central Subfield Thickness (CST) Variability Predicts Legal Blindness in Wet AMD[1]



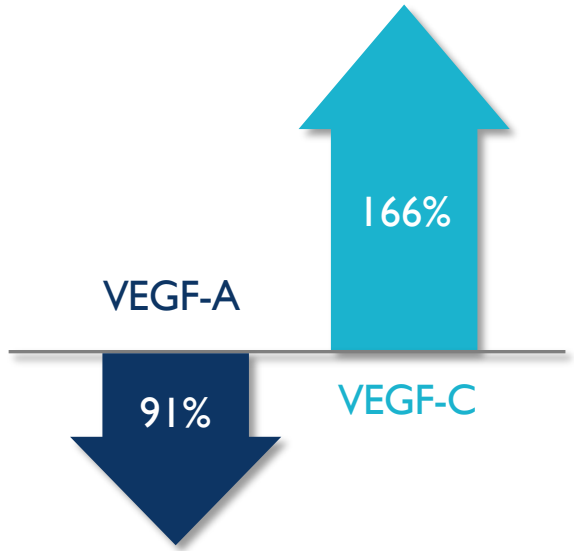
*Higher CRT variability during the first year of treatment is associated with **greater vision loss**[1] & **fibrosis**[2]*

1. Guo et al. *Ophthal Res* 2023; 66:406-12. 2. Evans et al. *JAMA Ophtalmol* 2020;138:1043-51. High variability: coefficient ≥20% in first year. Overall visual preservation rate: time from first injection to legal blindness (≤35 ETDRS letters). CRT, central retinal thickness.

4D-150 Solution: Dual-Transgene Payload Targeting 4 VEGF Family Members (VEGF-A, -B, -C & PlGF)

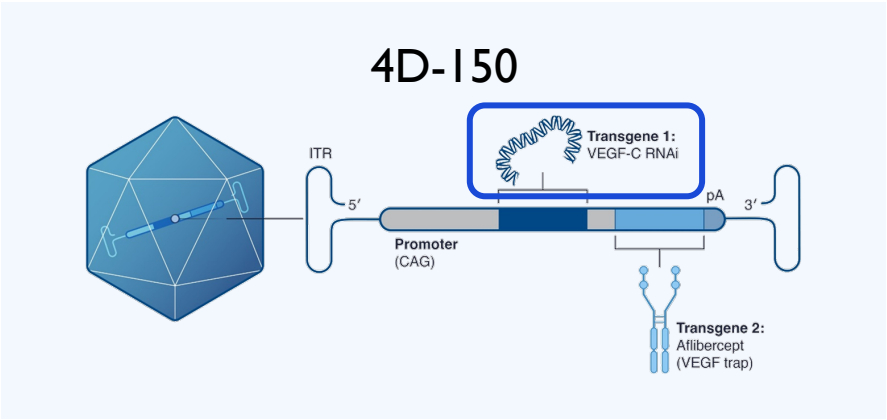
Biological Rationale for Targeting VEGF-C

Aqueous Concentrations Following Bevacizumab Injections[1]*



- Highly expressed in human RPE choroidal neovascular membranes[2]
- Stimulates endothelial cell proliferation and migration, vascular permeability[3–6]
- Upregulated by inhibition of VEGF-A[1,7,8]
- Potential anti-VEGF escape mechanism

4D-150: Dual-Transgene Payload



- Aflibercept
  Inhibits VEGF-A, VEGF-B, & PlGF
- VEGF-C miRNA
  Inhibits expression of VEGF-C

1. Cabral et al. *Ophthalmol Retina* 2018;2:31–7. 2. Otani A et al. *Microvasc Res* 2002;64:162–9. 2. Hsu MC et al *Cells* 2019;8. 3. Joukov et al. *EMBO J* 1996;15:290–8. 4. Joukov et al. *J Cell Physiol* 1997;173:211–15. 5. Cao Ret al. *Circ Res* 2004;94:664–70. 6. Puddu et al. *Mol Vis* 2012; 18:2509–177. Pongsachareonnont P et al. *Clin Ophthalmol* 20187;12:1877–85. 9. Jackson TL et al. *Ophthalmology* 2023 Feb 6: Epub. *2 months post administration of bevacizumab. RPE, retinal pigment epithelium.

4D-150 Poised to be Market Leader for VEGF-Driven Retinal Diseases

Designed to Address the Limitations of Current Therapeutic Regimens: VISION PRESERVATION

1

~80% of physicians cite therapeutic **durability** as the greatest unmet need [1]

✓ **Single** routine intravitreal injection provides durable clinical activity

2

Oscillating peak-trough anti-VEGF concentrations between injections can lead to **variability in CST**

✓ **Continuous** local expression of anti-VEGF transgenes to reduce CST variability

3

Treatment with VEGF-A inhibitors results in **increased VEGF-C levels in the eye**[2]

✓ **Dual** transgene payload targeting 4 VEGF family members (*VEGF-A, B, C & PlGF*)

Goal: **Vision Preservation** for Millions with a **Safe, Routine, One-time IVT Treatment**

1. 2023 ASRS PAT survey. 2. Cabral et al. *Ophthalmol Retina* 2018;2:31-7. CRT, central retinal thickness.

4D-150 Clinical Program Overview: Wet AMD & DME

Favorable Safety Profile & No Significant Inflammation Reported to Date (N=110)[1]

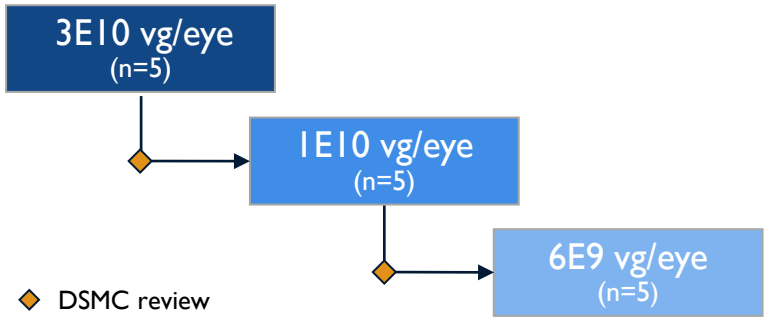
INDICATION	PATIENT POPULATION	PHASE 2 TRIALS	ENROLLMENT STATUS (PATIENTS DOSED[1])	PHASE 3 TRIAL
Neovascular (wet) Age-Related Macular Degeneration (AMD)	Severe Disease & High Treatment Burden	PRISM Dose Exploration & Expansion	**Complete** (N=15 & 41) **Follow-up: up to 104 weeks**	Target Initiation **Q1 2025**
	Broad	PRISM Population Extension	**Complete** (N=32) **Follow-up: up to 20 weeks**	
Diabetic Macular Edema (DME)	Broad	SPECTRA Part 1: Dose Confirmation	**Complete** (N=22) **Follow-up: up to 8 weeks**	*tbd*
		SPECTRA Part 2: Dose Expansion	*Pending* (N=54)	

1. Data cutoff date, January 19, 2024

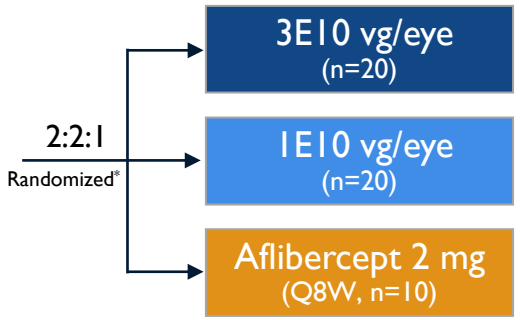
PRISM Phase 1/2 Clinical Trial is Evaluating 4D-150 in a Broad Range of Wet AMD Patient Populations

Severe Disease Activity & High Treatment Burden

Dose Exploration (Phase 1)



Dose Expansion (Phase 2)



Enrollment Began Jan 2023, Completed Jul 2023

Key Inclusion Criteria

- **Anti-VEGF Injections prior 12 months:** ≥6
- **CST at Screening:** ≥300 µm OR presence of subretinal or intraretinal fluid
- **BCVA:** 25–78 ETDRS letters (20/320-20/32)

Key Inclusion Criteria

- **Anti-VEGF Injections prior 12 months:** ≥6
- **CST at Screening:** ≥325 µm AND presence of subretinal or intraretinal fluid
- **BCVA:** 34–83 ETDRS letters (20/200-20/25)

Broad Disease Activity

Population Extension (Phase 2)

Enrollment Began Sep 2023 Completed Nov 2023

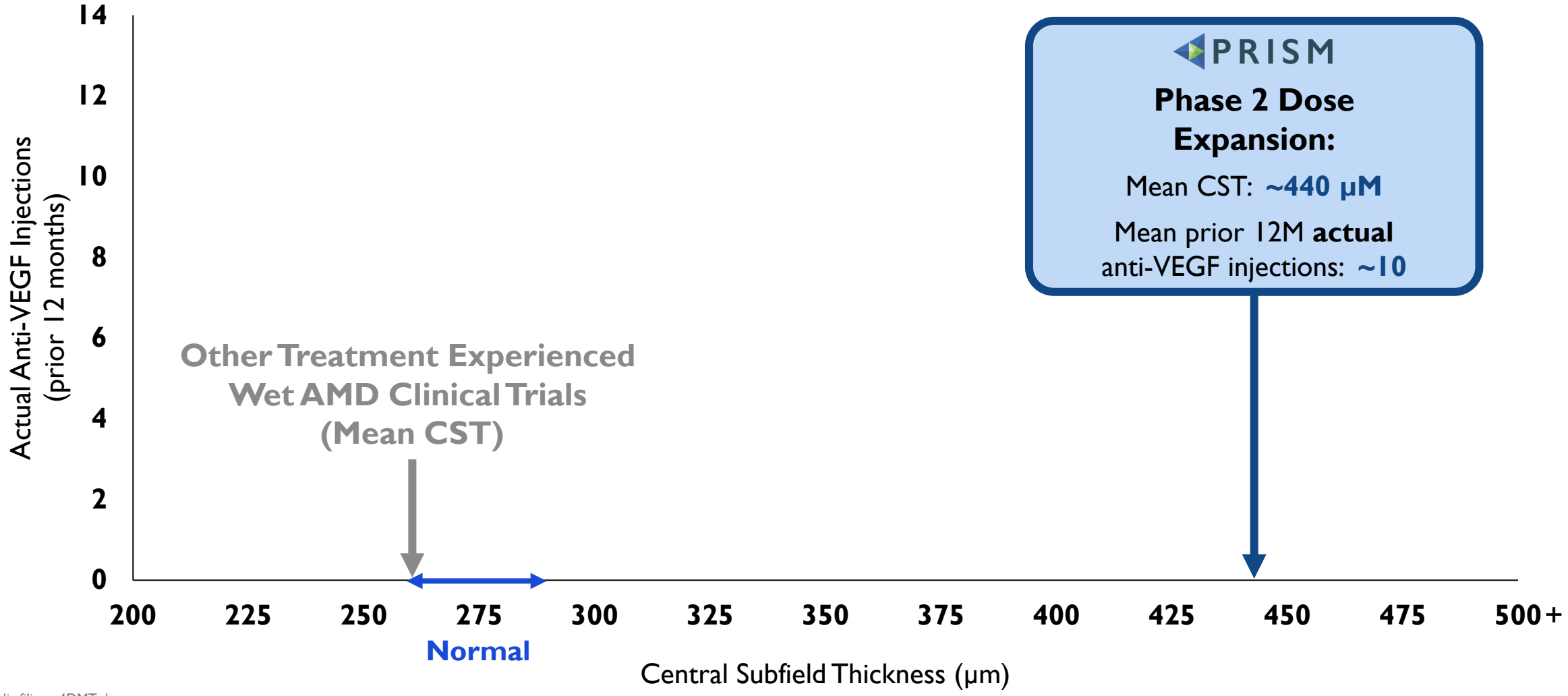
24-Week Interim Update Planned at ASRS in July 2024

Key Inclusion Criteria

- **Anti-VEGF Injections prior 12 months:** 1-6, ≥1 in last 12 weeks
- **CST at Screening:** historical response to anti-VEGF by SD-OCT confirmed by reading center
- **BCVA:** 34–83 ETDRS letters (20/200-20/25)

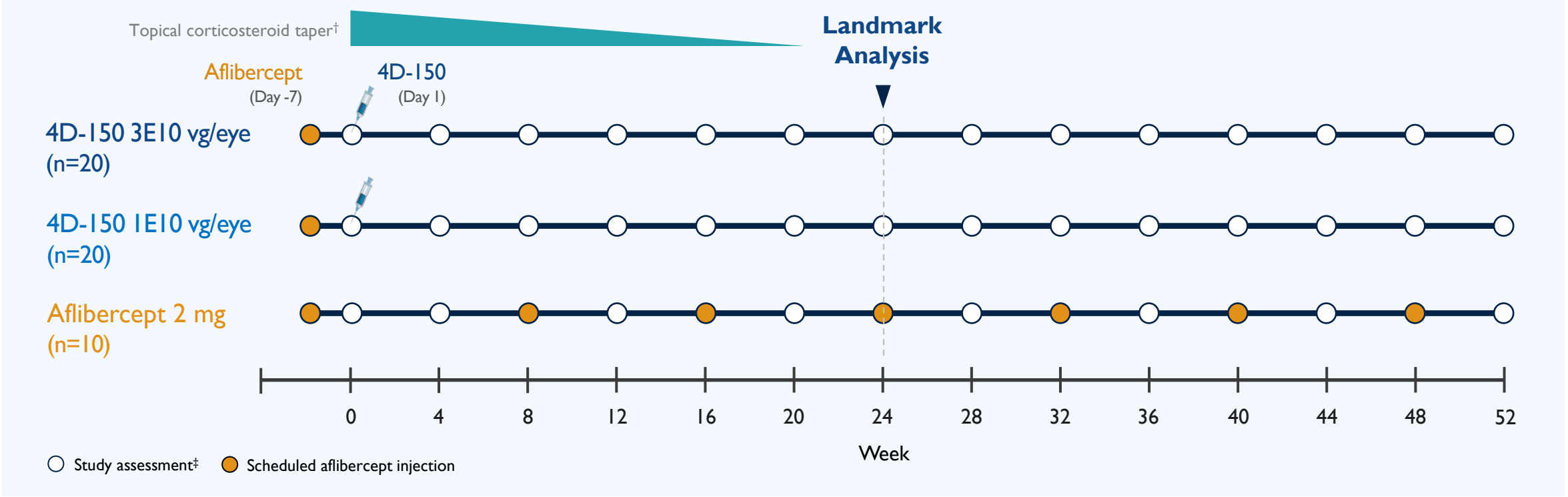
* Stratified by prior injections <9 vs. ≥9. BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

Initial Focus on Wet AMD Patients with Severe Disease Activity (CST) & Highest Treatment Burden (Actual Injections in Prior 12 Months)



Public filings, 4DMT data.

Phase 2 Dose Expansion Treatment Schema & Endpoints: 4D-150 at Doses of 3E10 & 1E10 vg/eye vs. Aflibercept Q8 Week Control



Supplemental Injection Criteria

- BCVA: Loss of ≥10 letters from average of Day -7 & Day 1 measurement attributable to intraretinal or subretinal fluid
- CST: Increase ≥75 µm from average of Day -7 & Day 1 measurement
- New vision-threatening hemorrhage due to wet AMD per investigator

Key Endpoints

- Safety
- Annualized anti-VEGF injection rate*
- % requiring supplemental aflibercept
- ΔBCVA and ΔCST from baseline

*Powered to detect difference in anti-VEGF injections compared to aflibercept; study participants and site personnel masked to 4D-150 dose (treatment assignment to 4D-150 vs aflibercept not masked).
†Scheduled 20-week corticosteroid taper (4D-150 groups). ‡Visual acuity, optical coherence tomography, ophthalmic exam.

Baseline Characteristics: Wet AMD Patients with Severe Disease Activity & High Treatment Burden

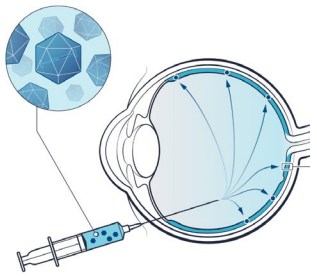
	3E10 vg/eye (n=20)	1E10 vg/eye (n=21)	Aflibercept (n=10)	**Total (N=51)**
Mean ±SD age, years	77 ± 8.0	77 ± 8.6	80 ± 4.1	77 ± 7.7 *(range: 57–92)*
Mean ±SD time since diagnosis, years (% ≥3 years)	4.0 ± 3.0 (60%)	2.9 ± 2.2 (33%)	1.9 ± 1.5 (20%)	3.1 ± 2.5 (41%) *(range: 0.7–11.1)*
Mean ±SD BCVA, ETDRS letters	68 ± 11.3	71 ± 12.4	71 ± 13.2	70 ± 11.9 *(range: 35–87)*
Mean ±SD central subfield thickness, µm	429 ± 89.3	465 ± 114.1	419 ± 64.3	**442** ± 96.9 *(range: 295–816)*
Mean *annualized* anti-VEGF injections*	10.0	9.9	9.0	**9.8**
Mean ±SD *actual* anti-VEGF injections in prior 12 months*	9.9 ± 2.4	9.4 ± 2.1	9.3 ± 0.9	**9.6** ± 2.0 *(range: 7–14)*

*Includes Day -7 AFLB injection
Data cutoff date, January 19, 2024

PRISM Met All Objectives in Wet AMD Patients with Severe Disease Activity & High Treatment Burden Through 24 Weeks

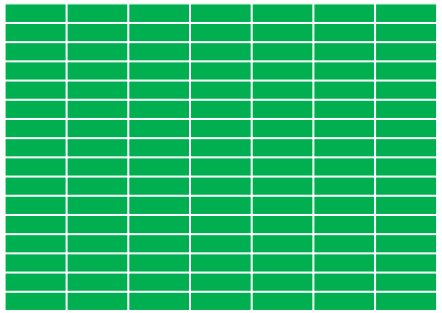
Administration

✓ **Single, routine** intravitreal injection



Safety

✓ **Favorable** safety profile; no significant or recurrent inflammation



Anti-VEGF Treatment Burden Reduction (3E10 vg/eye)

✓ **89%** overall reduction

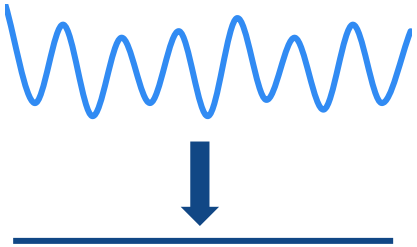
✓ **84%** 0–1 injections

✓ **63%** injection-free

Retinal Anatomical Control

✓ **Improved** retinal anatomical control

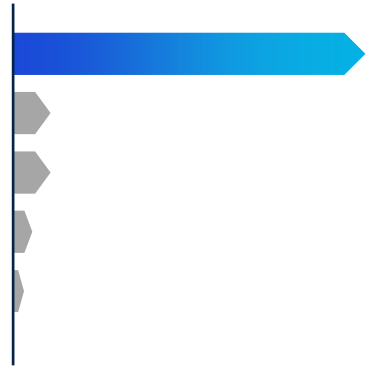
Retinal Thickness



Long Term Durability (3E10 vg/eye from Phase 1)

✓ **Multi-year** (up to 2 years) durability

Potential for long-term vision preservation



Data cutoff date, January 19, 2024

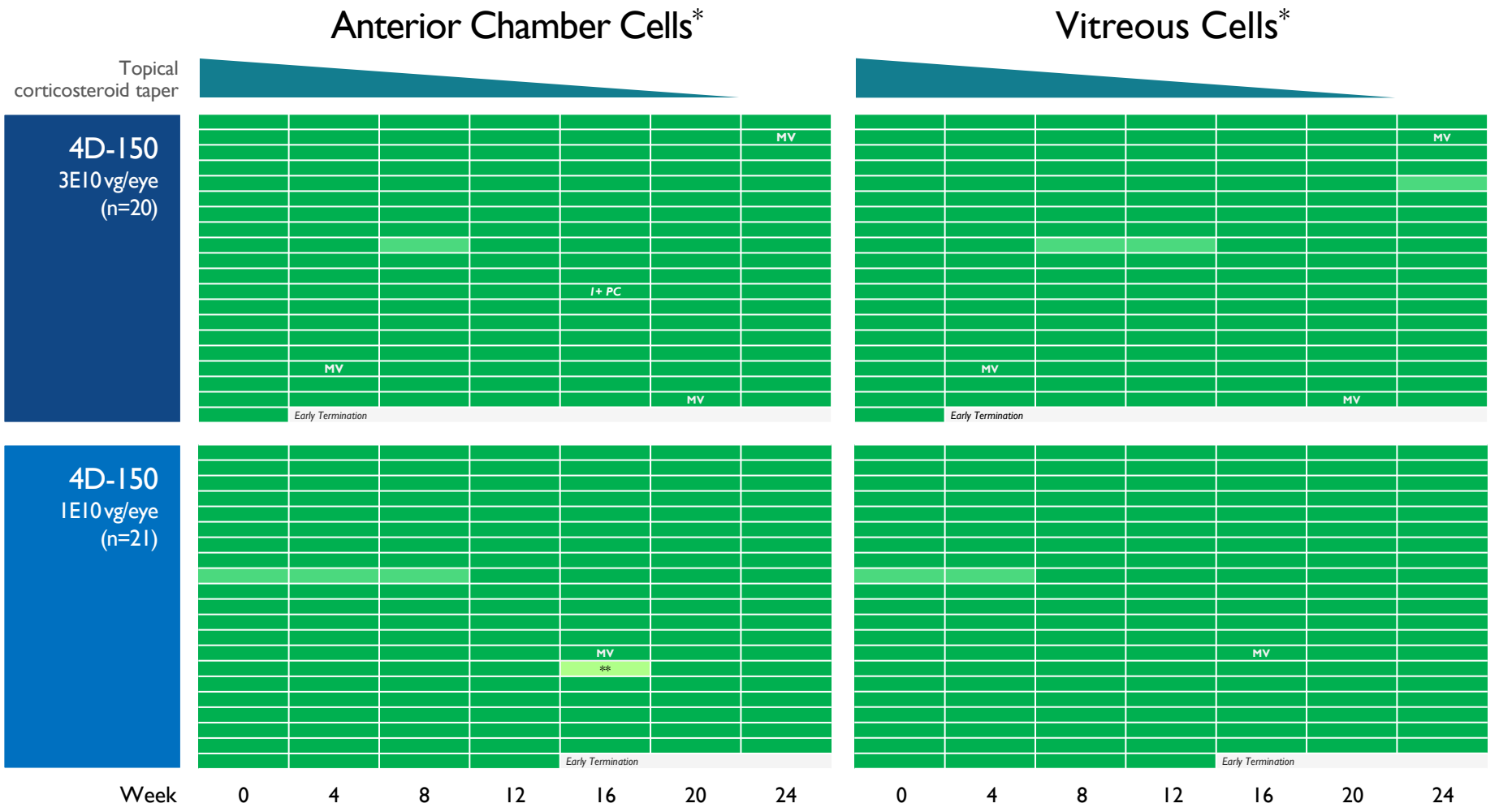
4D-150 Demonstrated Favorable Safety Profile to Date with No Significant or Recurrent Intraocular Inflammation

- **No significant intraocular inflammation***
  - **High dose (3E10 vg/eye): None**
  - **97% (38 of 39 patients) completed 20-week prophylactic topical corticosteroid taper on schedule**
  - Low dose: Single eye at week 16 had 1+ AC mixed (pigmented & white blood) cells and resolved by next visit; completed prophylactic topical corticosteroid taper by week 26
  - **All patients currently off steroids through up to 48 weeks of follow-up**
- No 4D-150–related SAEs or study eye SAEs
- No hypotony, endophthalmitis, retinal vasculitis, choroidal effusions, or retinal artery occlusions

Note: 2 patients died on study; PI assessed as not related to 4D-150 (3E10 vg/eye cohort: 1 subject died 38 days post 4D-150 IVT due to metastatic urothelial carcinoma;1E10 vg/eye cohort: 1 subject died 110 days post 4D-150 IVT due to acute myocardial infarction)

*SUN or NEI ≥1+ white blood cells on ophthalmic exam. AC, anterior chamber; SUN, Standardization of Uveitis Nomenclature; SAE, Severe Adverse Event.
Data cutoff date, January 19, 2024

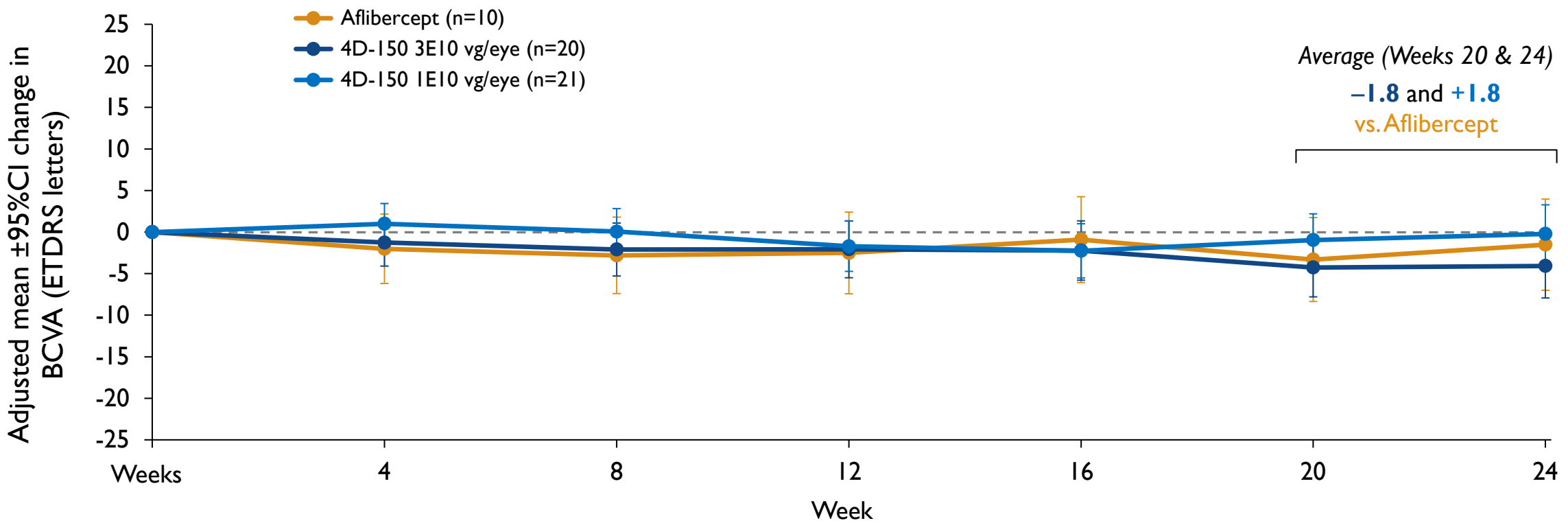
No Clinically Significant or Recurrent Intraocular Inflammation by Ophthalmic Examination



- 97% (38 of 39) completed 20-week corticosteroid taper on schedule
  - Single participant** had an increase in topical corticosteroid, completed taper by week 26
- No patients restarted steroids during follow-up for up to 48 weeks

*SUN and NEI Scores for white blood cells. **Mixed WBC and pigmented cells; managed with temporary increase in topical corticosteroid dose (taper completed by Week 26).
MV, missed visit. NEI, National Eye Institute; SUN, Standardization of Uveitis Nomenclature. Data cutoff date, January 19, 2024

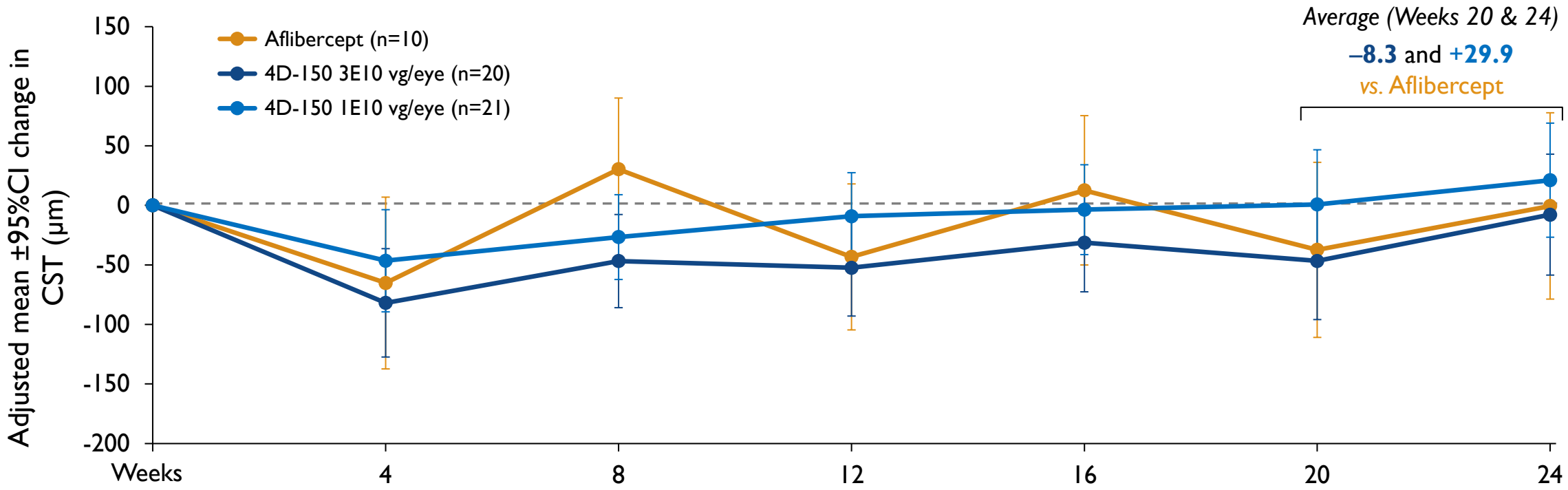
BCVA Equivalent & Stable Across All Arms in Severe Disease Activity Patients



Difference (95% CI) vs Aflibercept	Week 20	Week 24
4D-150 (3E10 vg/eye)	–1.0 (–7.2, 5.3)	–2.6 (–9.3, 4.2)
4D-150 (1E10 vg/eye)	2.3 (–3.6, 8.3)	1.3 (–5.2, 7.8)

Baseline=Day -7. BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.
Adjusted mean, difference in adjusted mean and the associated 95% CI are estimated from a mixed–effect model for repeated measures (MMRM) including Weeks 4-24 data as observed without imputing missing values.
Data cutoff date, January 19, 2024

High Dose 4D-150: Strong Anatomic Control at All Timepoints, Reduced CST Variability Compared to Aflibercept Arm



Difference (95% CI) vs Aflibercept	Week 20	Week 24
4D-150 (3E10 vg/eye)	–9.3 (–97.9, 79.3)	–7.3 (–101, 86.2)
4D-150 (1E10 vg/eye)	38.1 (–48.9, 125.2)	21.7 (–70.4, 113.8)

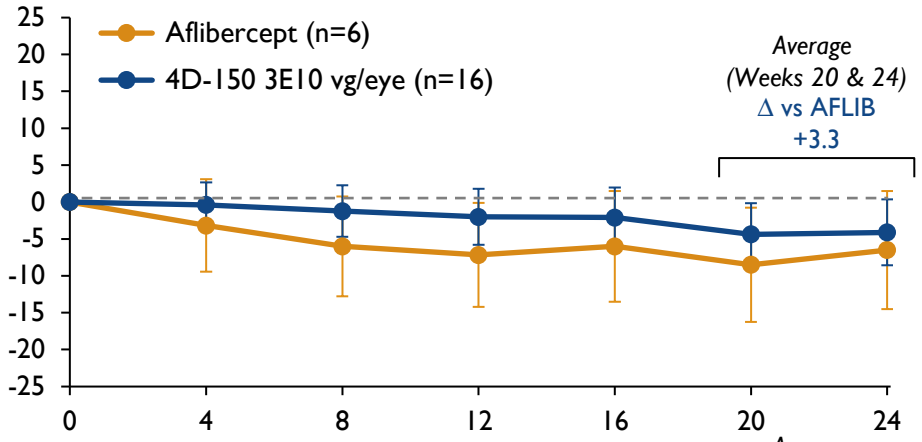
Baseline=Day -7. Adjusted mean, difference in adjusted mean and 95% CI estimated from a mixed–effect model for repeated measures including observed data (weeks 4-24) without imputing missing values. CST, central subfield thickness; CI, confidence interval. Data cutoff date, January 19, 2024

4D-150 High Dose: Vision and CST Outcomes Under Preliminary Phase 3 Eligibility Criteria* Supports Advancement to Phase 3

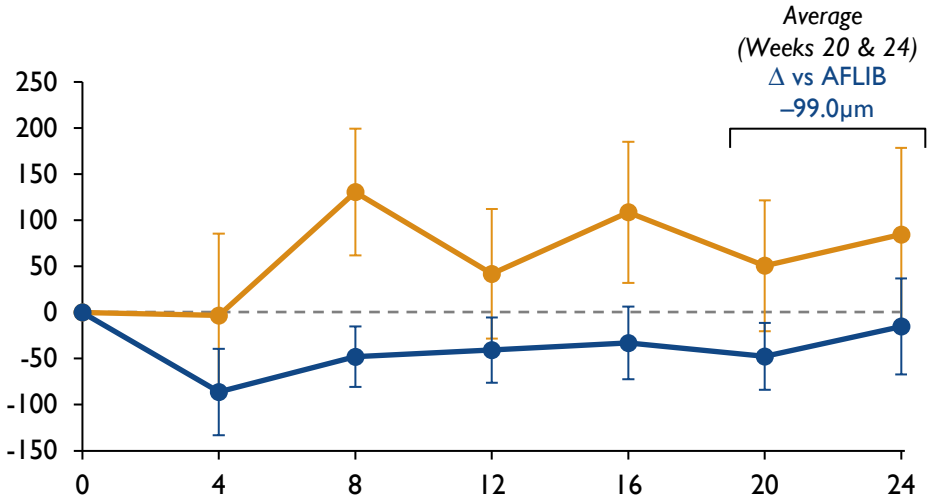
Preliminary Phase 3 Eligibility Criteria:

- CST: ≤500 µm
- BCVA: 40–78 ETDRS letters
- No serous PED >350 µm

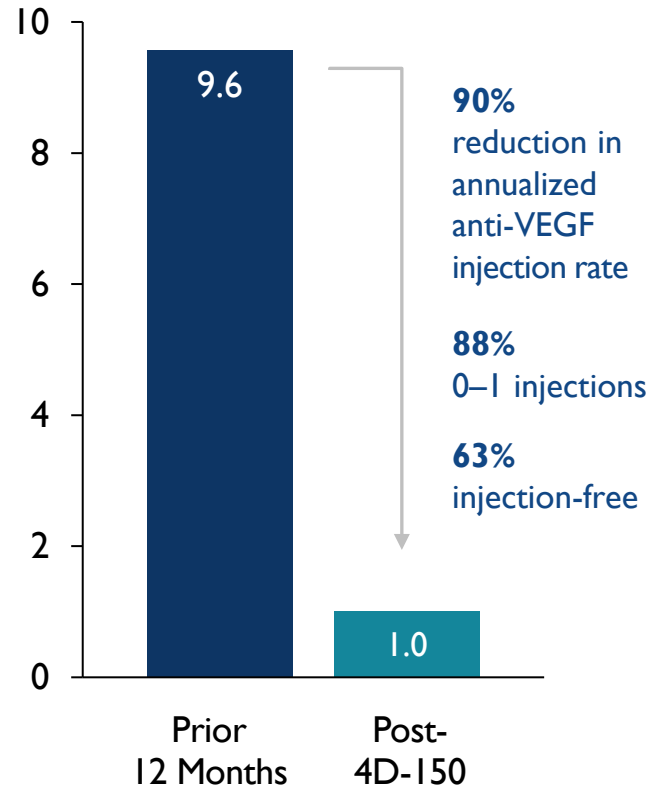
Adjusted mean ±95% CI change in BCVA (ETDRS letters)



Adjusted mean ±95% CI change in CST (µm)

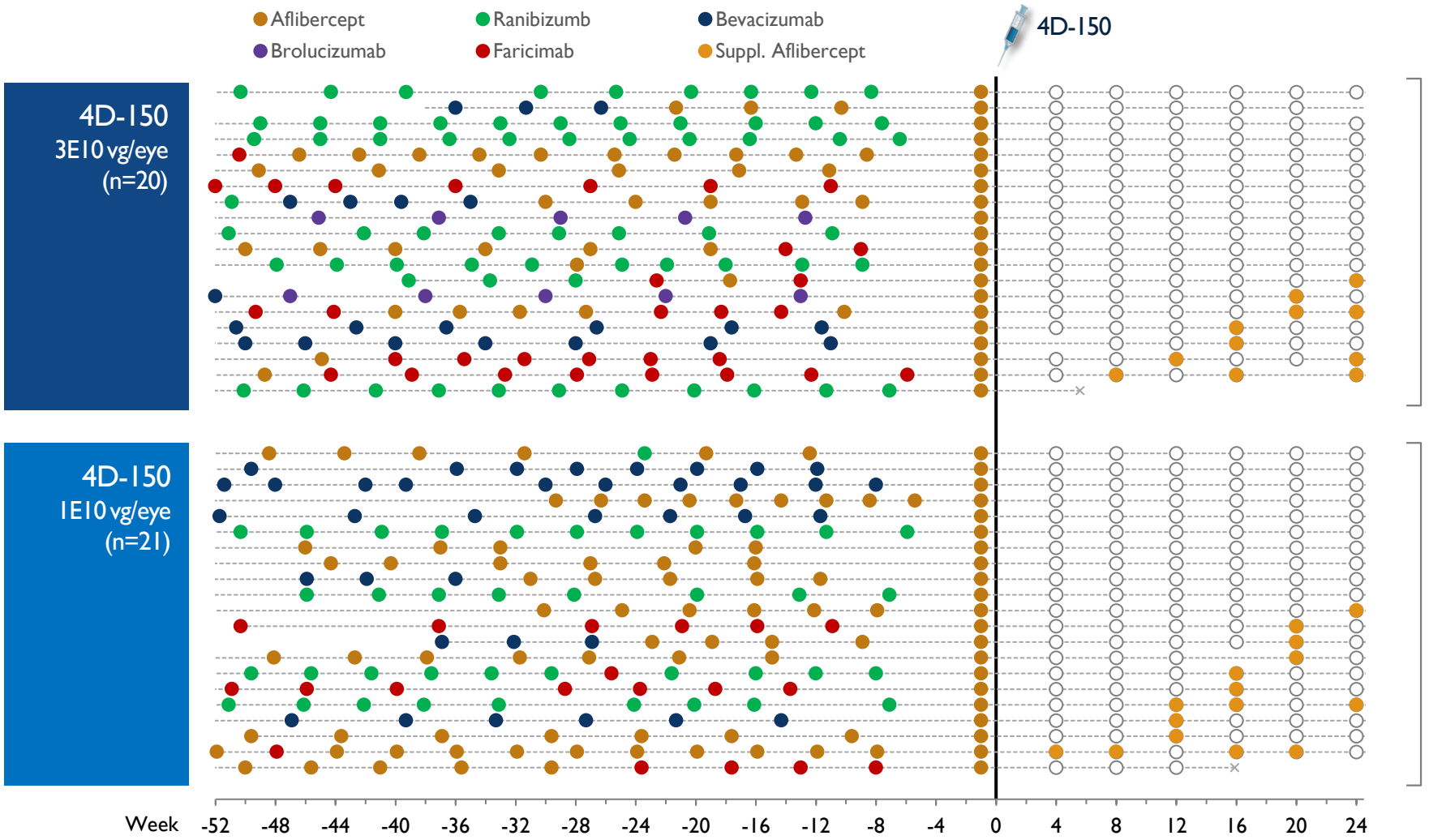


Anti-VEGF Injections



Baseline=Day -7. Adjusted mean, difference in adjusted mean and the associated 95% CI are estimated from a mixed–effect model for repeated measures (MMRM) including Weeks 4-24 data as observed without imputing missing values. *Participants excluded based on BCVA <40 or >78 ETDRS letters (n=6), CST >500 mm (n=1), or both BCVA <40 or >78 ETDRS letters and CST >500 mm (n=1). BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; CST, Central Subfield Thickness.
Data cutoff date, January 19, 2024

Robust Reduction in Treatment for Severe Disease Activity & High Treatment Burden Patients: 89% Reduction with High Dose 4D-150



89% reduction in annualized anti-VEGF injection rate

84% 0–1 injection

63% injection-free

85% reduction in annualized anti-VEGF injection rate

90% 0–1 injection

50% injection-free

Data cutoff date, January 19, 2024

PRISM Phase 1 Update: Tolerability & Durable Biological Activity Maintained for up to 104 Weeks in Injection-Free Patients

- **Safety (N=15)**: **maintained** (no new inflammation, no change in steroid status)
- **Durability of activity for 3E10 vg/eye injection-free patients (n=3):**
  - **All 3 patients remain injection-free**
    - Patient 1: through **104 weeks**
    - Patient 3: through **100 weeks**
    - Patient 4: through **80 weeks**

Data cutoff date, January 19, 2024

4D-150 Registrational Planning in Wet AMD

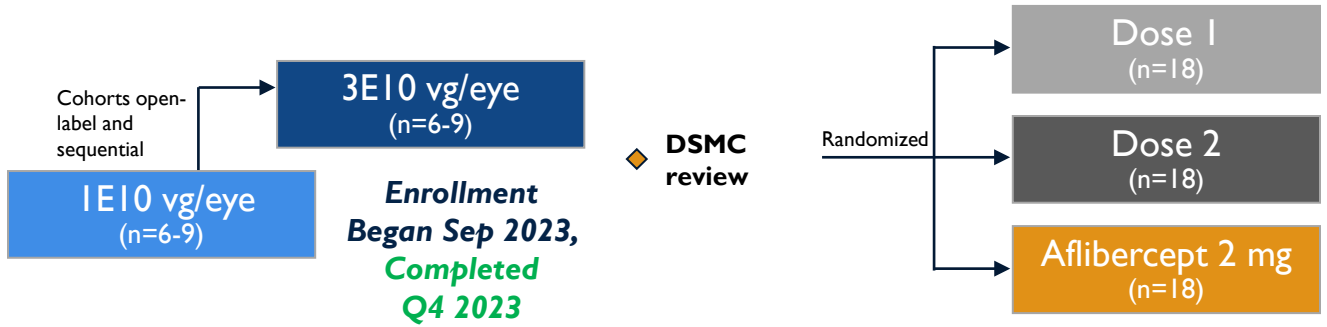
- **Phase 3 design based on initial feedback from FDA & EMA and clinical data to-date:**
  - Noninferiority (BCVA) 4D-150 **vs.** aflibercept 2mg Q8 week
  - **4D-150 3E10 vg/eye selected as study dose**
  - ~225 patients per arm
  - Broad wet AMD population, including patients with severe disease activity and high treatment burden
- **FDA RMAT & EMA PRIME Designations**
  - **Increased collaboration** between the FDA & EMA on regulatory approval planning
  - Opportunity for **expedited product development**
- Update on Phase 3 clinical trial design **expected in Q3 2024**
- **Expect to initiate first Phase 3 clinical trial in Q1 2025**

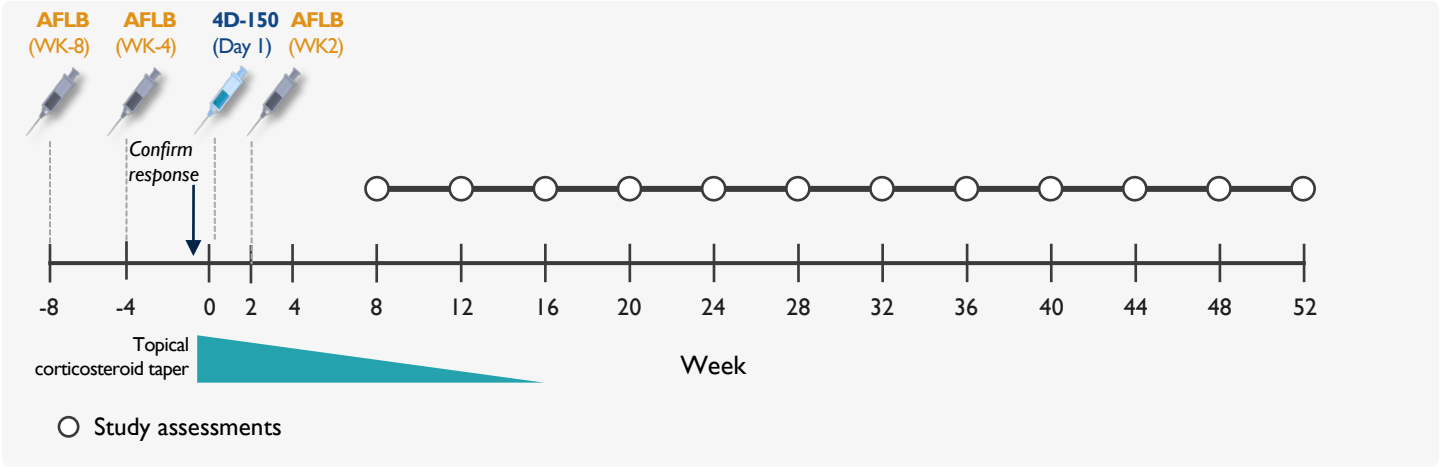
Phase 2 Study Evaluating 4D-150 in Diabetic Macular Edema, a 2nd Large Market Indication

Randomized, Active-Controlled, Double-Masked Phase 2

Part 1 – Dose Confirmation

Part 2 – Expansion





Key Inclusion Criteria

- Type I or II diabetes mellitus with macular thickening secondary to DME involving the center of the fovea
- BCVA: 25–83 ETDRS letters
- CST: ≥350 µm confirmed by independent reading center
- On-study anti-VEGF response prior to 4D-150 injection

Primary Endpoint

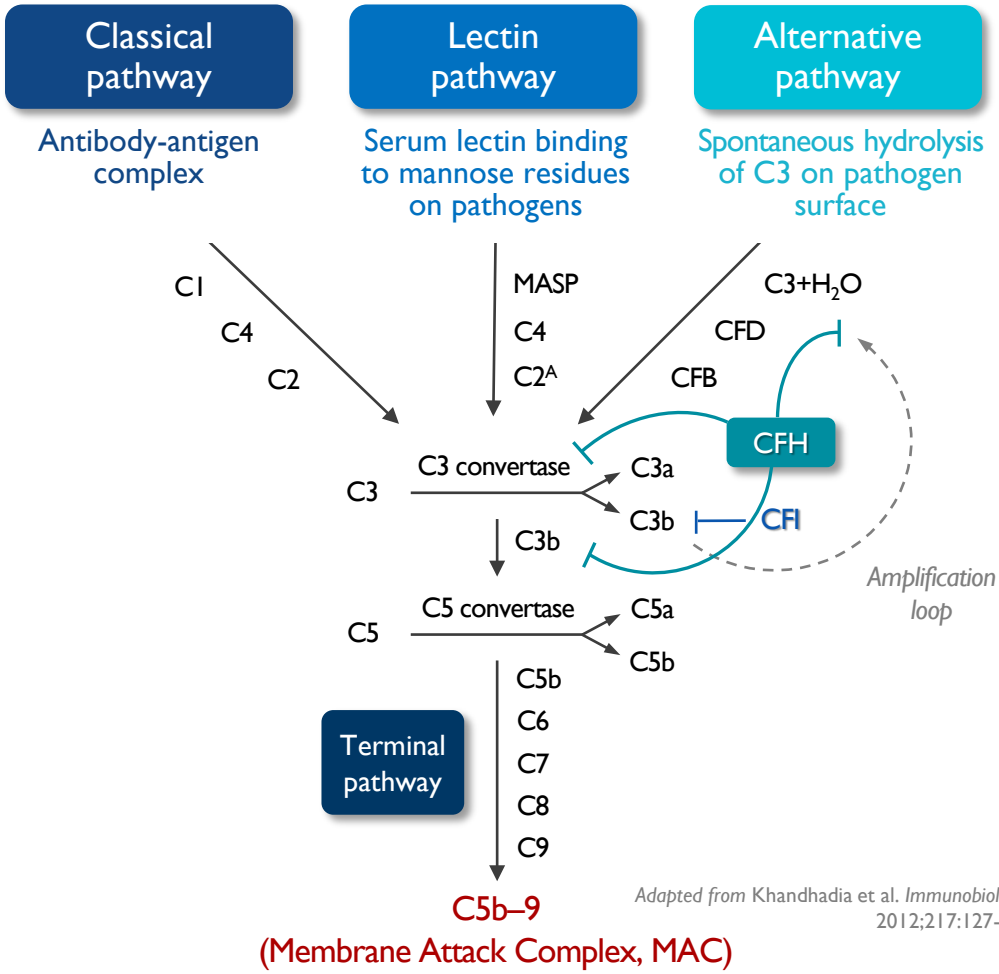
- Annualized number of aflibercept injections in the study eye

Key Secondary Endpoints

- Safety
- Mean cumulative number of aflibercept injections over time
- BCVA & CST: Δ from baseline
- % of subjects with a ≥2 and ≥3-Step Diabetic Retinopathy Severity (DRS) improvement from baseline

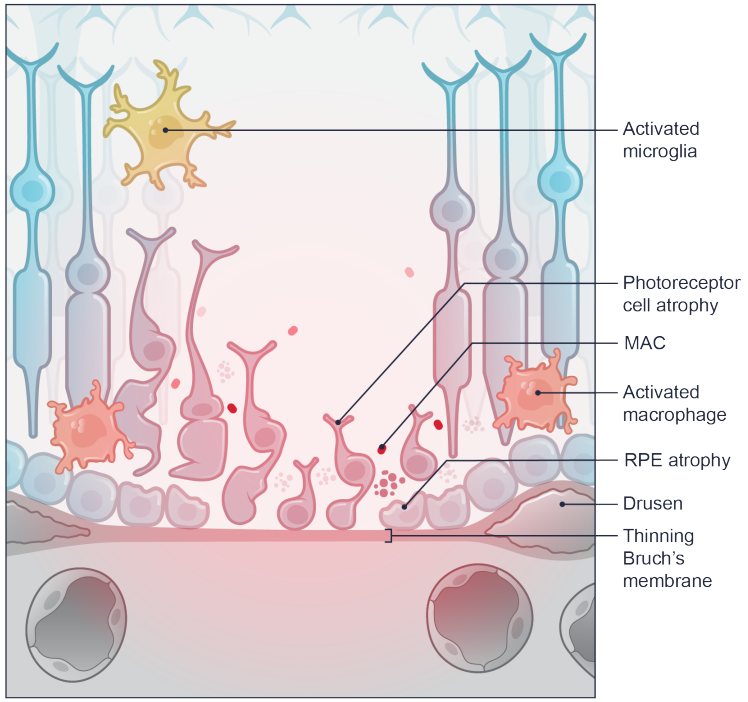
DME, Diabetic Macular Edema; BCVA, Best-Corrected visual acuity; CNV, choroidal neovascularization; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor

Geographic Atrophy is a Large and Growing Retinal Disease, CFH Dysfunction & Activation of the Complement Pathway Implicated



Adapted from Khandhadia et al. *Immunobiology* 2012;217:127-46.

Geographic Atrophy (GA)



- **~2.5 million** prevalence U.S./EUMM[1]
- CFH dysfunction amplifies activation of the **alternative complement pathway**[2,3]
  - CFH variants with reduced function are a validated genetic risk factor for GA, **~75%** of AMD patients carry a high-risk variant
- Current treatments reduce the rate of growth in GA lesions but **require monthly or bimonthly intravitreal injections**[4,5]

GA, geographic atrophy; EUMM, EU major markets; CFH, complement factor H; MAC, membrane attack complex; RPE, retinal pigment epithelium.

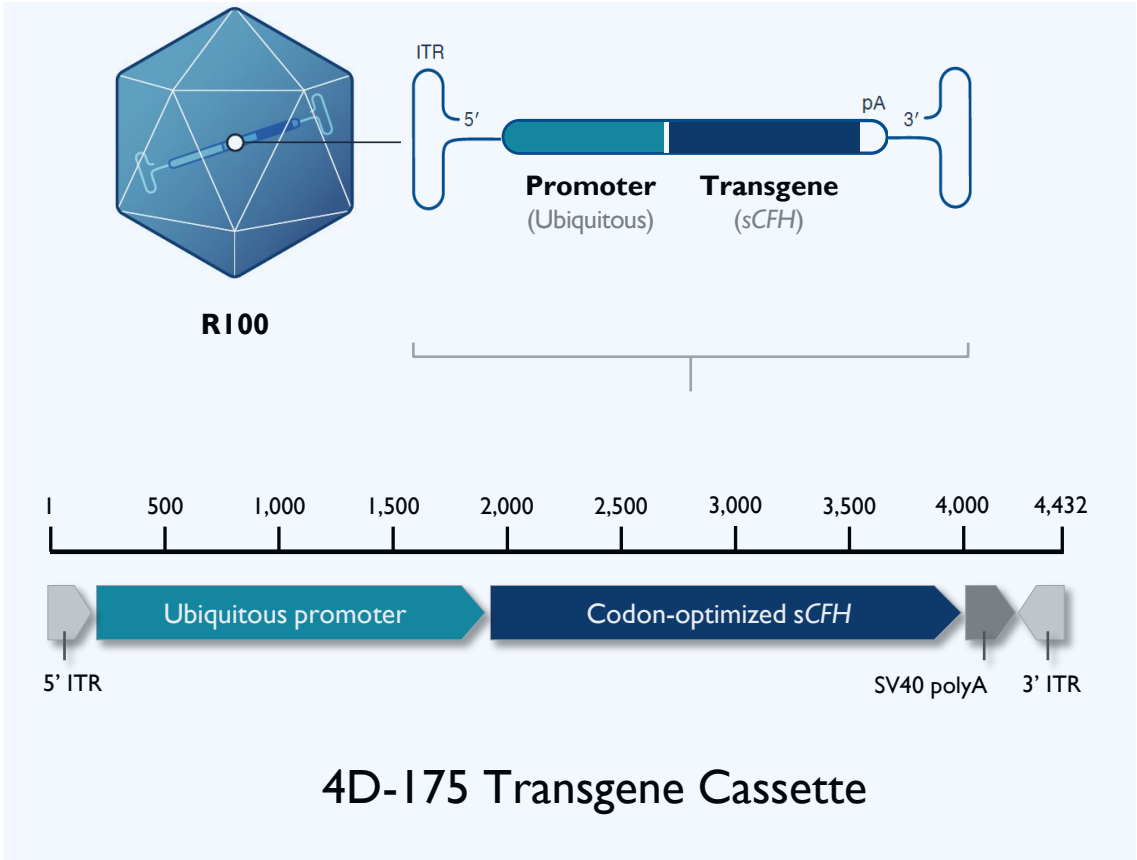
1. Rein, D. et al. *JAMA Ophthalmol*. 2022;140(12):1202-8 2. Manuelian et al. *J Clin Invest* 2003;111:1181–90. 3. Prosser et al. *J Exp Med* 2007;204:2277–83. 4. Syfovre [package insert]. Apellis Pharmaceuticals. 5. Izervay [package insert]. Iveric Bio, Inc.

4D-175 Solution: Intravitreal Gene Therapy for Geographic Atrophy

Biological Rationale

- **Clinically validated** retinotropic AAV vector (R100)
- Codon-optimized sequence encoding a highly functional, shortened form of human complement factor H (sCFH)
- Ubiquitous promotor to drive transgene expression
- **Therapeutic objective: Restore normal complement regulation** in the retina through **durable expression of sCFH**
  - **Phase 1 Dose Exploration expected to initiate in H2 2024**

4D-175: *sCFH*-Transgene Payload



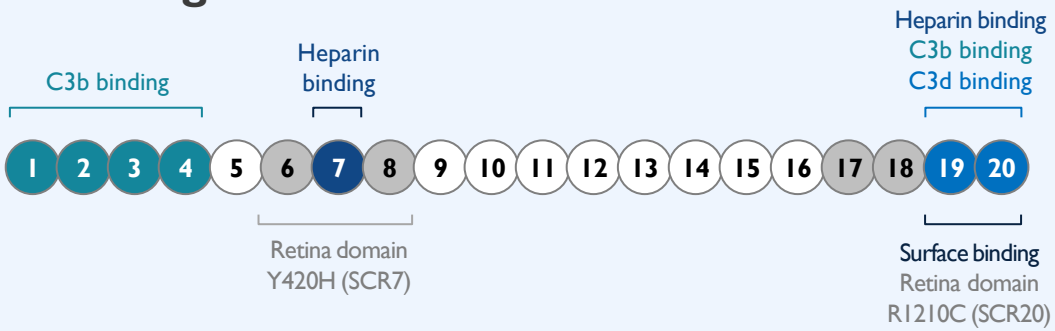
4D-175 Transgene Cassette

1. Moore et al. *IOVS* 2001;42:2970-5. 2. Bok et al. *IOVS* 1985;26:1659-94. GA, geographic atrophy; IVT, intravitreal; RPE, retinal pigment epithelium

Short-form Complement Factor H (sCFH) is Highly Functional Compared to Full-Length

Transgene Design

Full-length Human CFH[1]

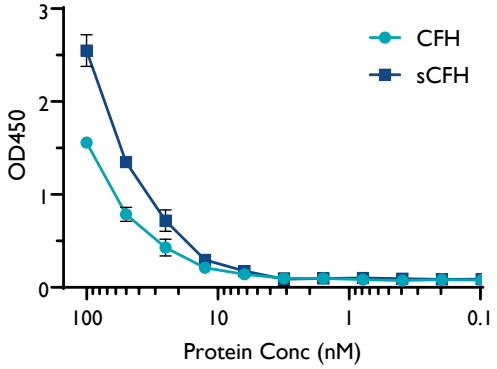


Short-form CFH (sCFH)

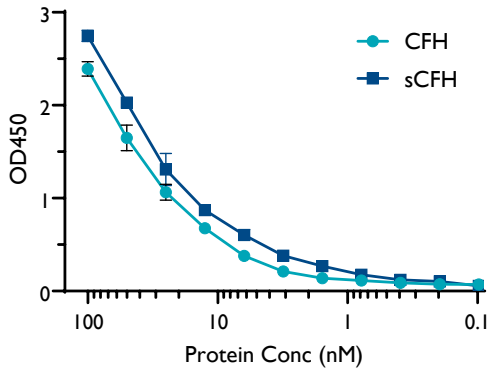
- Reduced size of the sCFH protein predicted to result in increased penetration of the RPE and choroid[2,3]

Pharmacological Activity

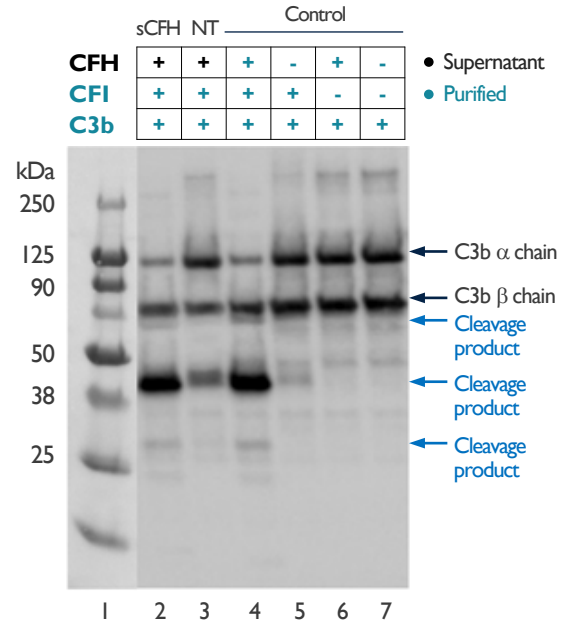
Heparin Binding



hC3b Binding



C3b Cleavage



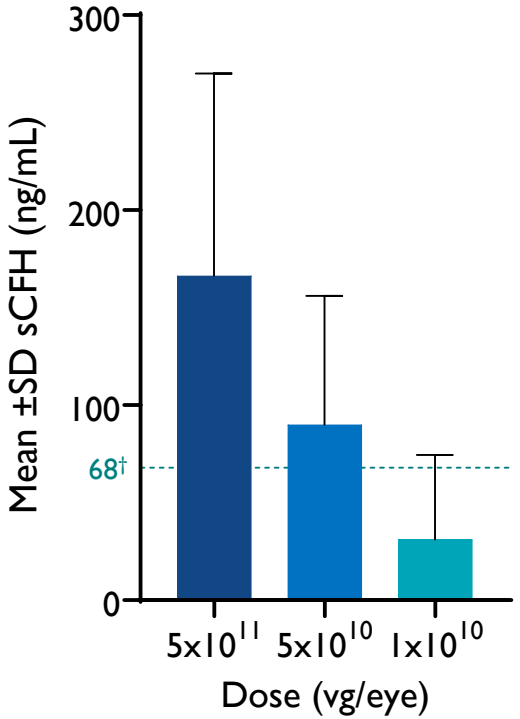
sCFH exhibits proper heparin and C3b binding and **inhibits complement activity *in vitro***

1. de Córdoba SR, de Jorge EG. Clin Exp Immunol 2008;151:1–13. 2. Moore et al. IOVS 2001;42:2970-5.
3. Bok et al. IOVS 1985;26:1659-94.

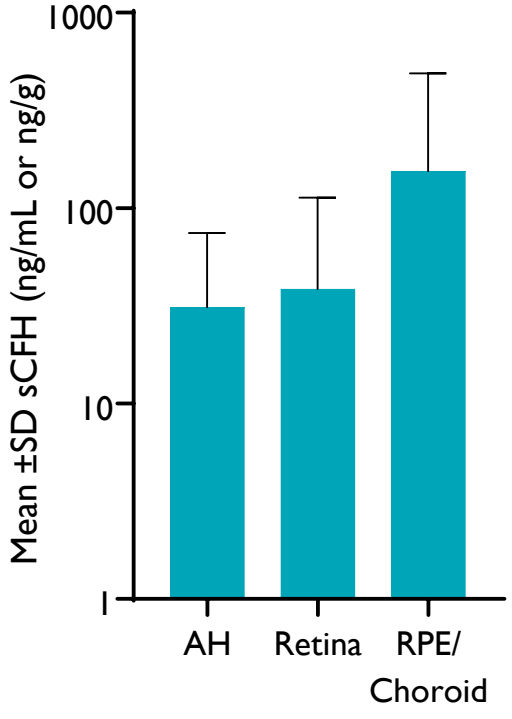
Target sCFH Concentration Levels Reached in Non-Human Primate Ocular Pharmacodynamics and Tolerability Study

4D-175 sCFH Ocular Biodistribution

Aqueous Humor*



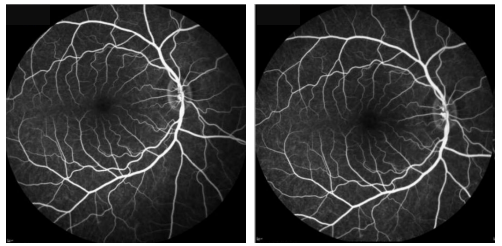
Ocular Distribution‡



4D-175 Safety and Tolerability

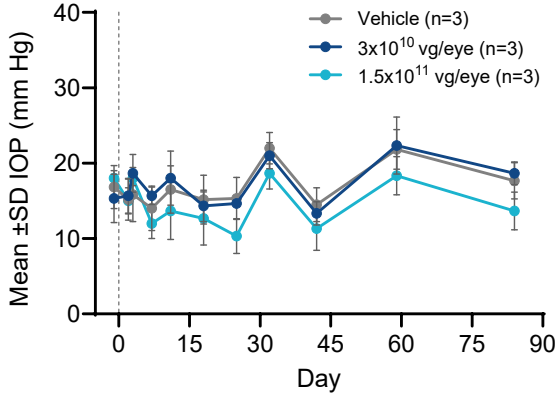
Fluorescein Angiography

NHP 2502 ($1.5x10^{11}$ vg/eye)



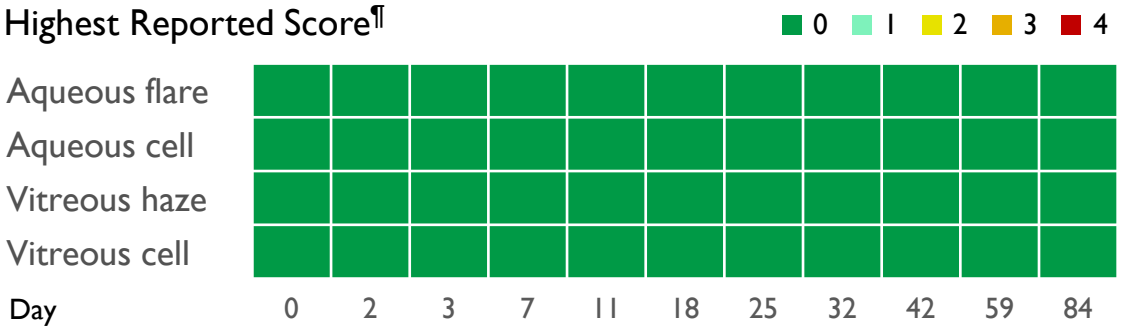
Baseline Week 12

Intraocular Pressure (IOP)



Ophthalmic Examination

Highest Reported Score¶



*Day 15 following IVT administration of 4D-175. †Target mean AH CFH concentration [1]. ‡$1x10^{10}$ vg/eye; tissue concentrations assessed at necropsy. ¶Uveitis score ($3x10^{10}$ and $1.5x10^{11}$ vg/eye; n=3 animals per group). 1. Altay et al. *Eye* 2019;33:1859–64.

Rapidly Advancing Development in Large Market Ophthalmology

VECTOR DELIVERY	PRODUCT CANDIDATE	INDICATION	EPIDEMIOLOGY (PREVALENCE)	IND-ENABLING	PHASE 1	PHASE 2	PHASE 3	EXPECTED UPCOMING MILESTONES
OPHTHALMOLOGY **R100** **Intravitreal** 	**4D-150** Aflibercept + VEGF-C RNAi	**Wet AMD**	*~3M U.S./EUMM*	PRISM				▪ **July 2024** Initial interim 24-week landmark analysis data from Phase 2 Population Extension (N=32) at ASRS ▪ **Q3:24** Update on Phase 3 clinical trial design ▪ **Q1:25** Initiate Phase 3 program
		Diabetic Macular Edema	*~5M U.S./EUMM*	SPECTRA				▪ **Q4:24** Initial interim 24-week landmark analysis from Phase 2 Dose Confirmation (N=22)
	4D-175 Short Form Complement Factor H	**Geographic Atrophy**	*~2.5M U.S./EUMM*					▪ **Q2:24** IND filing ▪ **H2:24** Phase 1 initiation

4DMT

PULMONOLOGY

Modular Vector: A101

- **4D-710:** Cystic Fibrosis Lung Disease
- **4D-725:** Alpha-1 Antitrypsin Deficiency Lung Disease

A101: Next-Gen Aerosolized Genetic Medicine Vector for Pulmonology

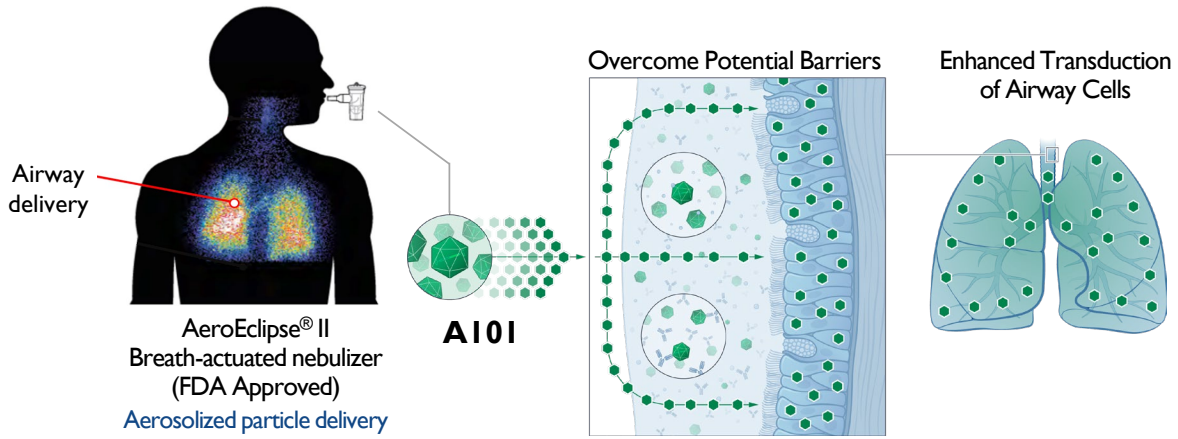
Prior aerosol gene therapy trials failed to achieve transgene expression in lung[1,2]; potential limitations:

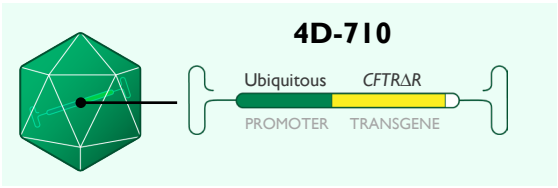
- ✕ Poor mucus penetration
- ✕ Inefficient airway cell transduction
- ✕ Suboptimal tissue tropism
- ✕ Susceptibility to clearance by antibodies

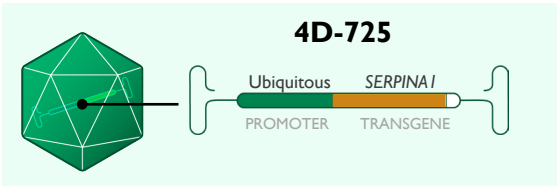
A101 invented at 4DMT to overcome these limitations:

- ✓ Mucus penetration efficient
- ✓ Transgene expression efficient
- ✓ Transduction of multiple airway cell types
- ✓ Specificity for lung (>99.9%)
- ✓ Resistance to pre-existing human AAV antibodies

Aerosolized A101-Based Genetic Medicines







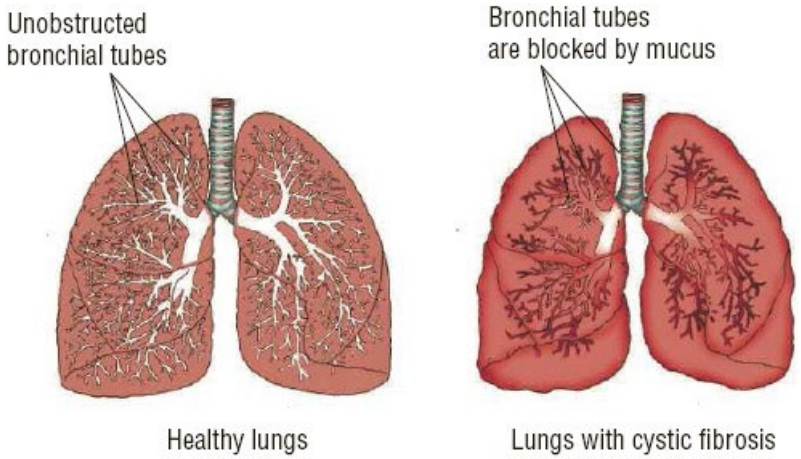
Product	Indication	Prevalence	Preclinical	Phase 1/2	Phase 3
4D-710	CF Lung Disease (monotherapy)	*~15K WW*			
	CF Lung Disease (w/ modulators)	*~90K WW*			
4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EU*			

1. Aitken ML et al. Hum Gene Ther 2001; 12:1907–16. 2. Moss RB et al. Chest 2004;125:509–21. 3. Moss RB et al. Hum Gene Ther 2007; 18:726 32.

CF Lung Disease Has High Unmet Medical Need Despite Modulators

Disease Burden

- **Dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) protein** → inability to transport chloride at the apical membrane → thickened mucus
- **Lung disease:** inflammation, infections, respiratory failure
- **Median survival (Pre-modulators):** ~40 years[1]



Epidemiology

- **~105,000[2,3] prevalence worldwide:**
  - ~40,000 prevalence in U.S. alone
  - ~1,000 incidence in U.S. alone

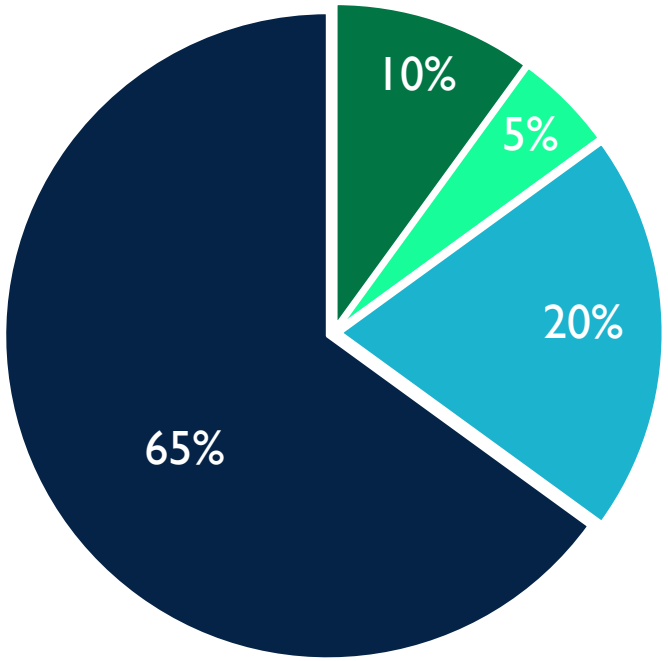
Standard of Care

- **Daily Supportive Care:**
  - Airway clearance (~100 mins)
  - Inhaled antibiotics & bronchodilators
- **Disease modifying CFTR modulators:**
  - **$9.9 billion** annually (2023)[4]

Illustration by Frank Forney. © 2016 Cengage Learning 1. Ramsey & Welsh. *Am J Respir Crit Care Med* 2017;195(9):1092–9. 2. Guo J et al. *Journal of Cystic Fibrosis* 2022; 21:456-62. 3. Cystic Fibrosis Foundation. 4. Vertex Pharmaceuticals FY 2023 financial results. CFTR, cystic fibrosis transmembrane conductance regulator.

Highest Unmet Need in ~35K People with Cystic Fibrosis

4D-710 has the Potential to Treat Cystic Fibrosis Lung Disease Regardless of Genetic Variant

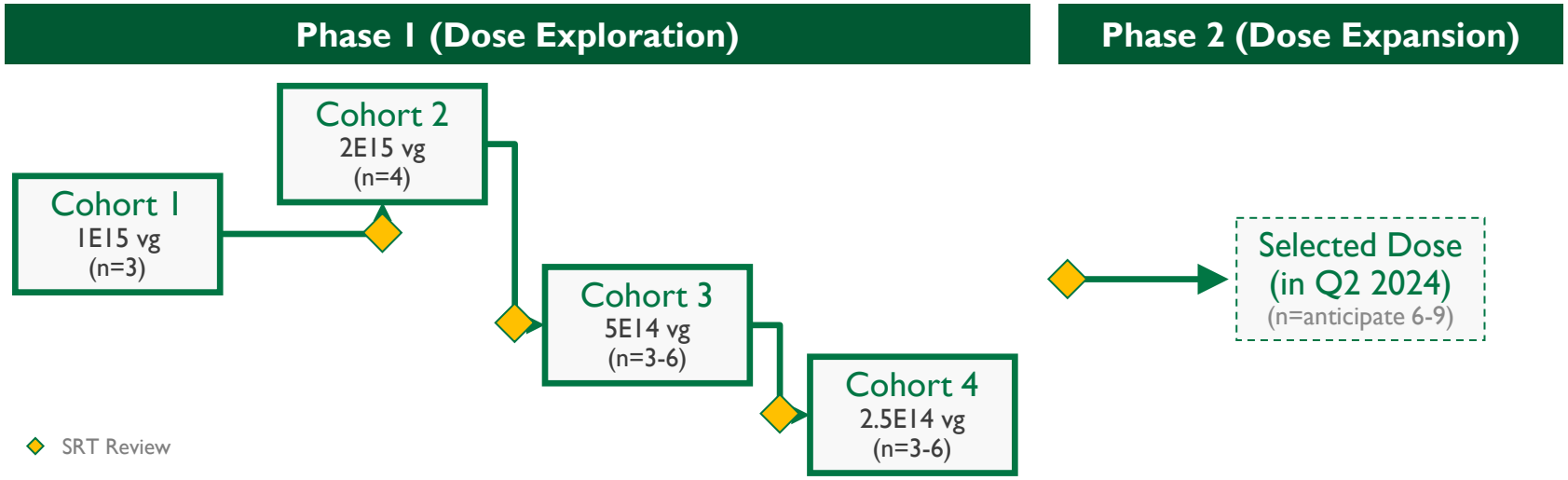
Cystic Fibrosis Population WW	Population Segment	Estimated People	
 ~105k	**Ineligible** for CFTR modulators	~10k	AEROW study population evaluating 4D-710 as **monotherapy**
	Intolerant to CFTR modulators	~5k	
	Suboptimal response to CFTR modulators[1]	~20k	Potential future 4D-710 study population
	Responsive to CFTR modulators	~70k	*Upside if superior dosing, efficacy, and/or safety is demonstrated*

~35k

CFTR, cystic fibrosis transmembrane conductance regulator. 1. Based on assumptions derived from Middleton, 2019 and CFF registry analysis.

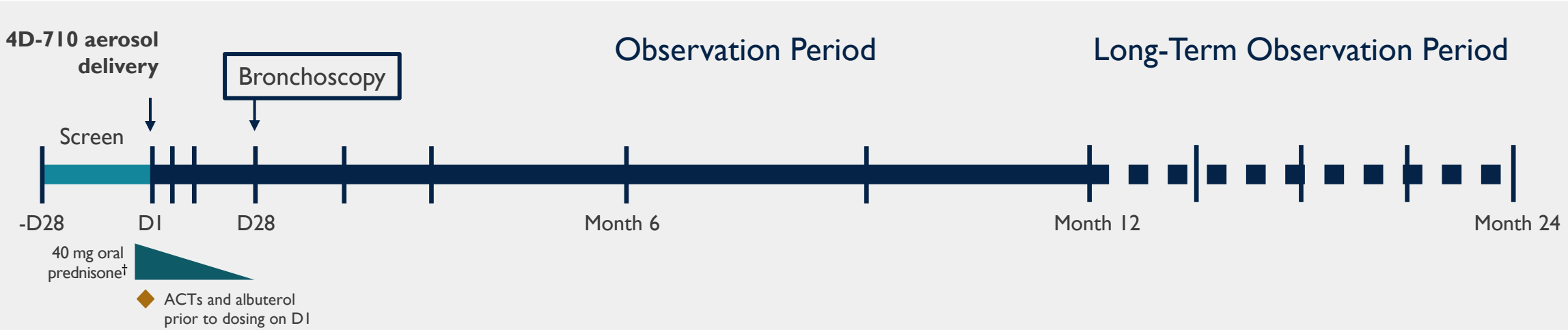
Phase 1/2 Designed to Identify Doses for Late-Stage Development

Generate Safety, Biomarker & Clinical Activity Data to Determine Phase 2 Dose



Key Endpoints:

- Safety & tolerability
- Lung biomarkers
- Clinical activity



Vertical bars represent study clinic visits. * Protocol allows for additional lower doses to be explored. † 28-day taper (Day -1 to Day 27). ACTs, Airway Clearance Techniques; SRT, Safety Review Team.

AEROW Enrolled Individuals with Generally Mild Baseline ppFEV$_1$ Impairment

2 Participants with Pre-Dosing NAbs to A101 Capsid

Characteristic	Cohort 1 (1E15 vg)			Cohort 2 (2E15 vg)			
	Participant 1	Participant 2	Participant 3	Participant 1	Participant 2	Participant 3	Participant 4
Age, y	36	24	20	37	27	32	69
Sex	Male	Male	Female	Female	Male	Female	Female
Race/ethnicity	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white	Non-Hispanic white
CFTR modulator eligibility	Intolerable	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Intolerant
CFTR variant (class)	II/V	I/I*	I/II	I/I	I/I	I/I	II/II
Historical sweat chloride, mmol/L	74	103	110	84	96	103	114
Percent predicted FEV$_1$	**83**	69	**95**	**90**	56	**80**	**86**
Quality of Life (CFQ-R-RD)	72	61	83	78	72	89	78
Pre-dose NAb to A101 capsid	**Positive**	Negative	**Positive**	Negative	Negative	Negative	*Pending*

*Large gene deletion projected to result in a null variant profile. Sweat chloride normal range ≤29 mmol/L, *Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation* (2017). CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R-R, Cystic Fibrosis Questionnaire–revised respiratory domain; NAb, neutralizing antibodies.

4D-710 Significantly Exceeded Target CFTR Expression Profile in Airways

Target CFTR Expression Profile	Biomarker Results from Cohorts 1 & 2
✓ **Widespread** distribution throughout airways	**Confirmed: 100%** of bronchoscopy samples (+) (34 of 34)*
✓ **Reproducibility** between individuals	**Confirmed: 7 of 7** participants
✓ **All major epithelial cell types** (incl. basal cells & secretory cells)	**Confirmed: 7 of 7** participants
✓ Robust expression **regardless of baseline antibody titer** (initial redosing feasibility)	**Confirmed: 2 of 2** participants with pre-treatment anti-capsid antibodies, **no decrease in transduction efficiency observed**
✓ **≥15% of airway cells transduced with CFTR**[1,2]	**Significantly Exceeded: >98%** of airway cells CFTR (+)
✓ **≥15% of normal CFTR protein levels**[1,2]	**Significantly Exceeded: ~450% of normal** CFTR protein levels

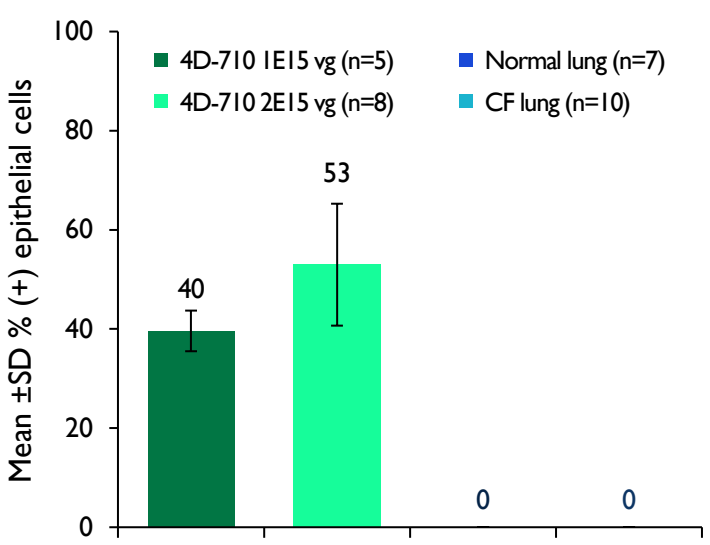
1. Dannhoffer L et al. Am J Respir Cell Mol Biol 2009; 40:717–23. 2. Bell S et al. Lancet Resp Med 2020; 8:65–124.*13/13 biopsy samples and 21/21 bronchial brushing samples. CFTR, cystic fibrosis transmembrane conductance regulator.

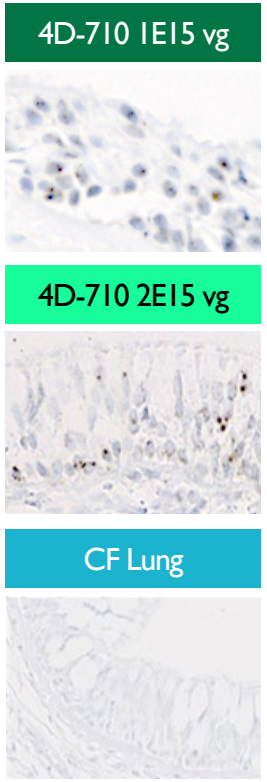
High-Level CFTR Expression in All 34 Lung Samples*

Robust 4D-710 Transgene Expression in Airway Epithelium Post Aerosol Delivery (7 Participants)

CFTRΔR RNA (ISH)

100% of samples (+) for *CFTRΔR* RNA

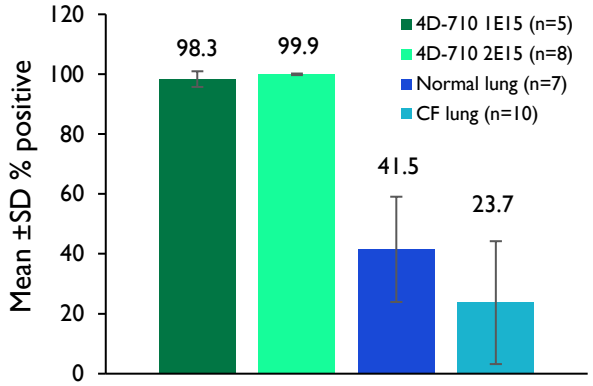


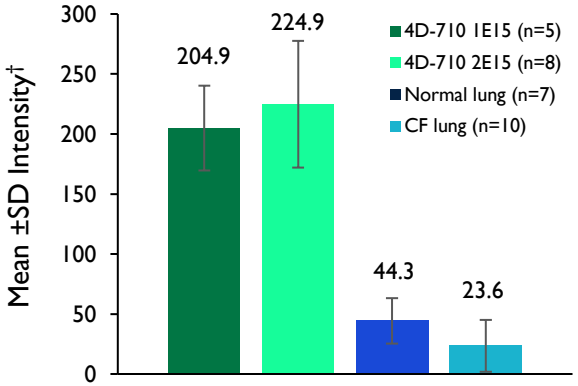


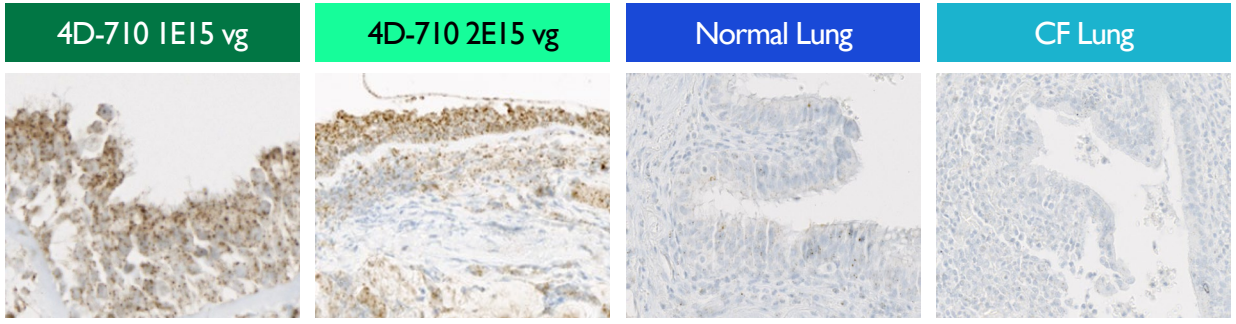
Robust levels of *CFTRΔR* RNA observed throughout the airway epithelium in biopsy samples from 4D-710–treated participants

CFTR Protein (IHC)

~100% of samples (+) for CFTR protein, **~450% of normal**





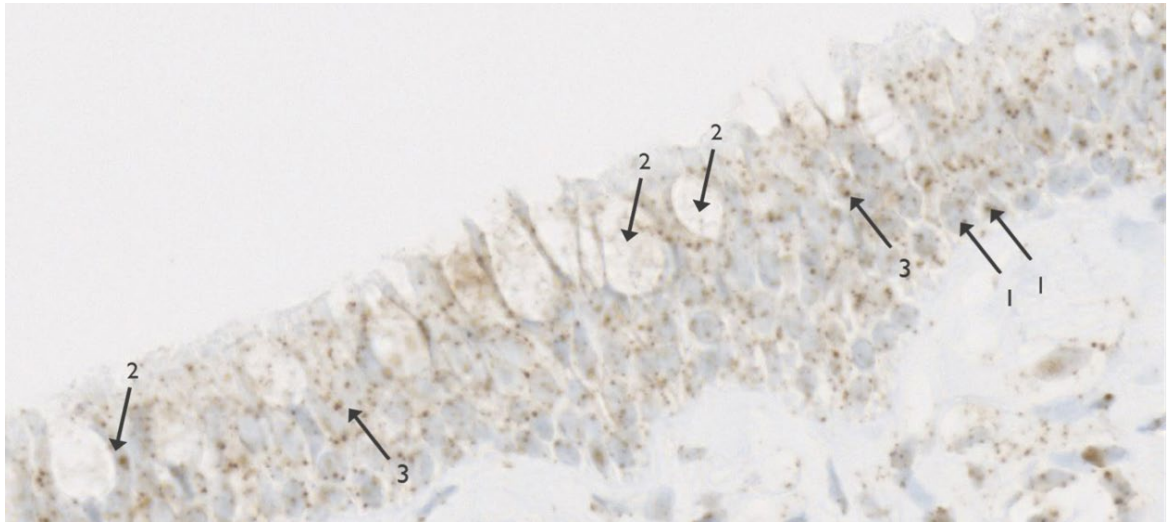


*13/13 biopsy samples and 21/21 bronchial brushing samples. †H-score. Quantification by Visiopharm AI Machine Learning Analysis. CFTR, cystic fibrosis transmembrane conductance regulator. IHC, immunohistochemistry; ISH, in situ hybridization; SD, standard deviation.

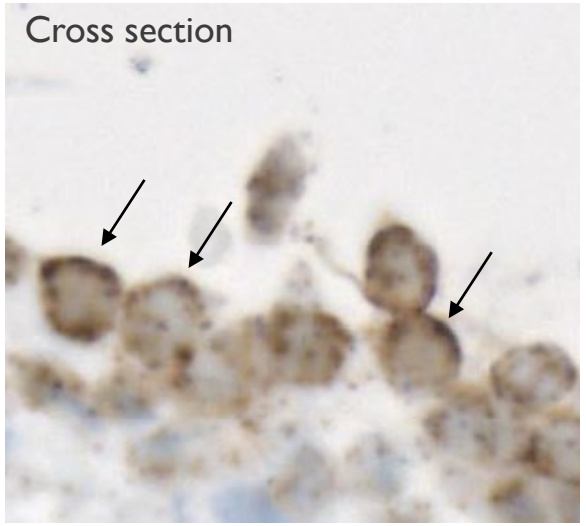
CFTR Protein Expression Observed in Multiple Bronchial Epithelial Cell Types

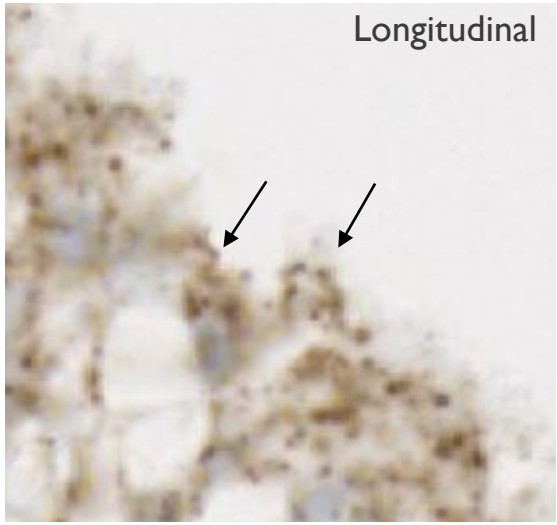
CFTR Protein Localization (IHC) Following 4D-710 Aerosol Treatment

CFTR Protein Expressed in Multiple Cell Types*



Localization to Apical Membrane†





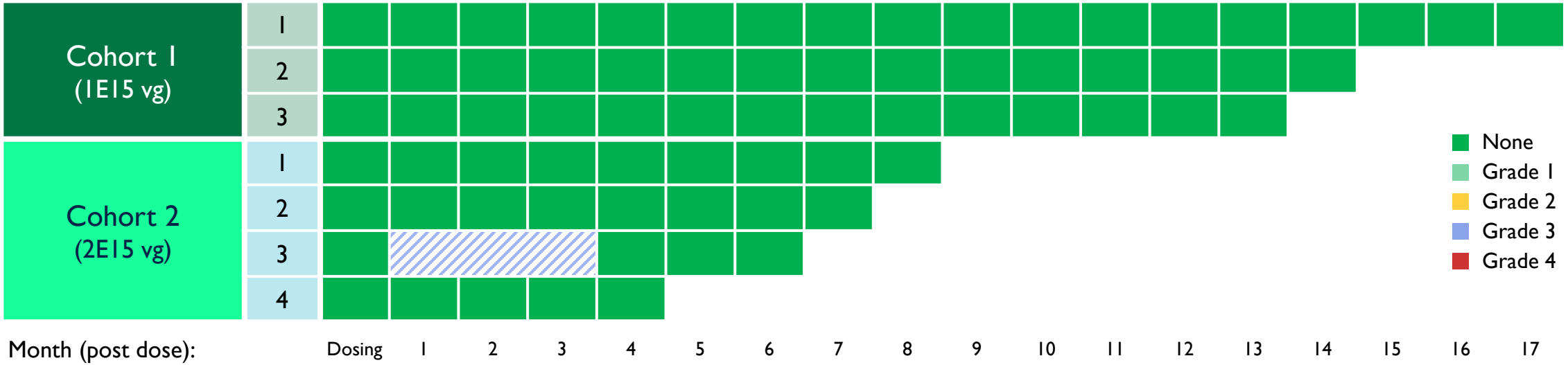
(**1**) Basal cells (**2**) Goblet cells (**3**) Columnar ciliated cells

*Image from Cohort 1 participant. †Images from Cohort 2 participants. CFTR, cystic fibrosis transmembrane conductance regulator. IHC, immunohistochemistry.

Generally Well Tolerated in 6 Participants with Up To 17 Months of Follow-Up

No Inflammation Observed in Airway Biopsies 4-8 Weeks Following 4D-710 Dosing

4D-710-Related Adverse Events During and Post-Dosing

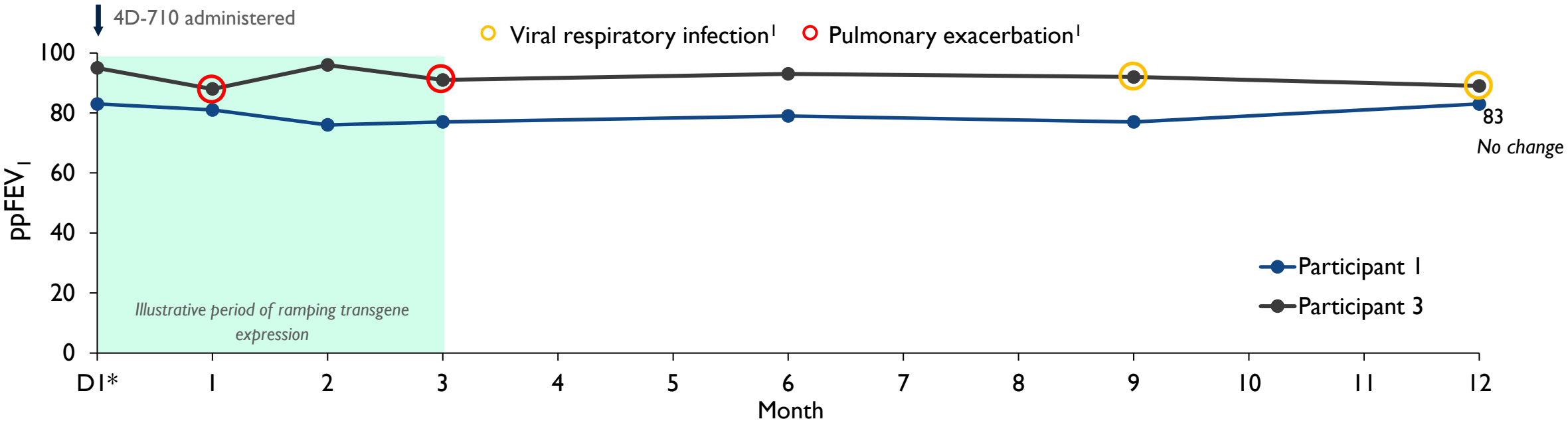


- No clinically significant AEs during aerosol administration of 4D-710
- Background: In NHP GLP Tox studies, no inflammation or toxicity observed at dose ~5-fold[1] higher than Cohort 2 dose
- No inflammation observed in any lung biopsy samples via 3rd party pathologist evaluation
- Cohort 1: no related AEs in 3 of 3 participants
- Cohort 2: no related AEs in 3 of 4 participants
  - Single SAE (hospitalization <72 hours; pneumonitis NOS) at week 3: Consistent with bacterial pneumonia

1. Human lung equivalent. NHP, non-human primate; GLP, good laboratory practices; AE, adverse event; SAE, severe adverse event; NOS, not otherwise specified.

Cohort 1: Durable ppFEV$_1$ Stabilization in Participants with **Mild/No** Lung Impairment

Stable Despite Pulmonary Exacerbations/Viral Respiratory Infections Not Related to 4D-710



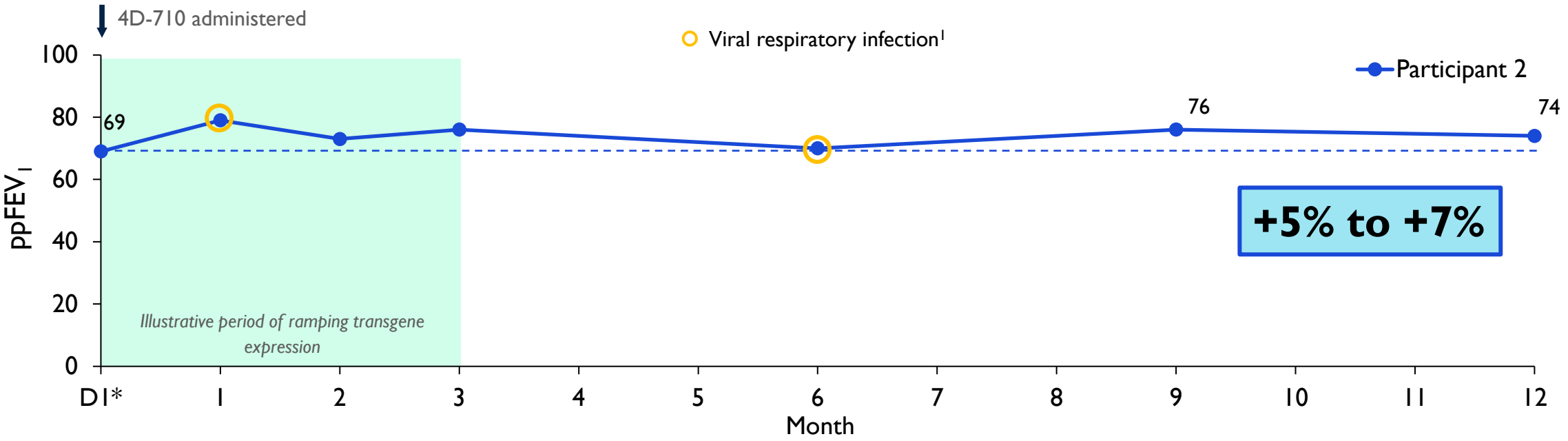
Start Day, Pulmonary Exacerbations/Viral Respiratory Infections (not related to 4D-710):

Cohort 1	Month 1	Month 3	Month 6	Month 9	Month 12	Beyond Month 12
Participant 1	**none**	**none**	**none**	**none**	**none**	**none** (through month 17)
Participant 3	Day 29: Grade 2 Infective PE	Day 81: Grade 1 Infective PE (*S. aureus*+)	**none**	Day 266: Grade 1 COVID-19	Day 329: Grade 1 Upper respiratory infection	**None** (through month 13)

1. Within 21 days of assessment. *Pre-dose spirometry assessment. ppFEV1, percent predicted forced expiratory volume in 1 second; PE, pulmonary exacerbation.

Cohort 1: Durable ppFEV$_1$ Improvement in Participant with **Moderate** Lung Impairment

Range +1 To +10 Over 12 Months



Start Day, Pulmonary Exacerbations/Viral Respiratory Infections (not related to 4D-710):

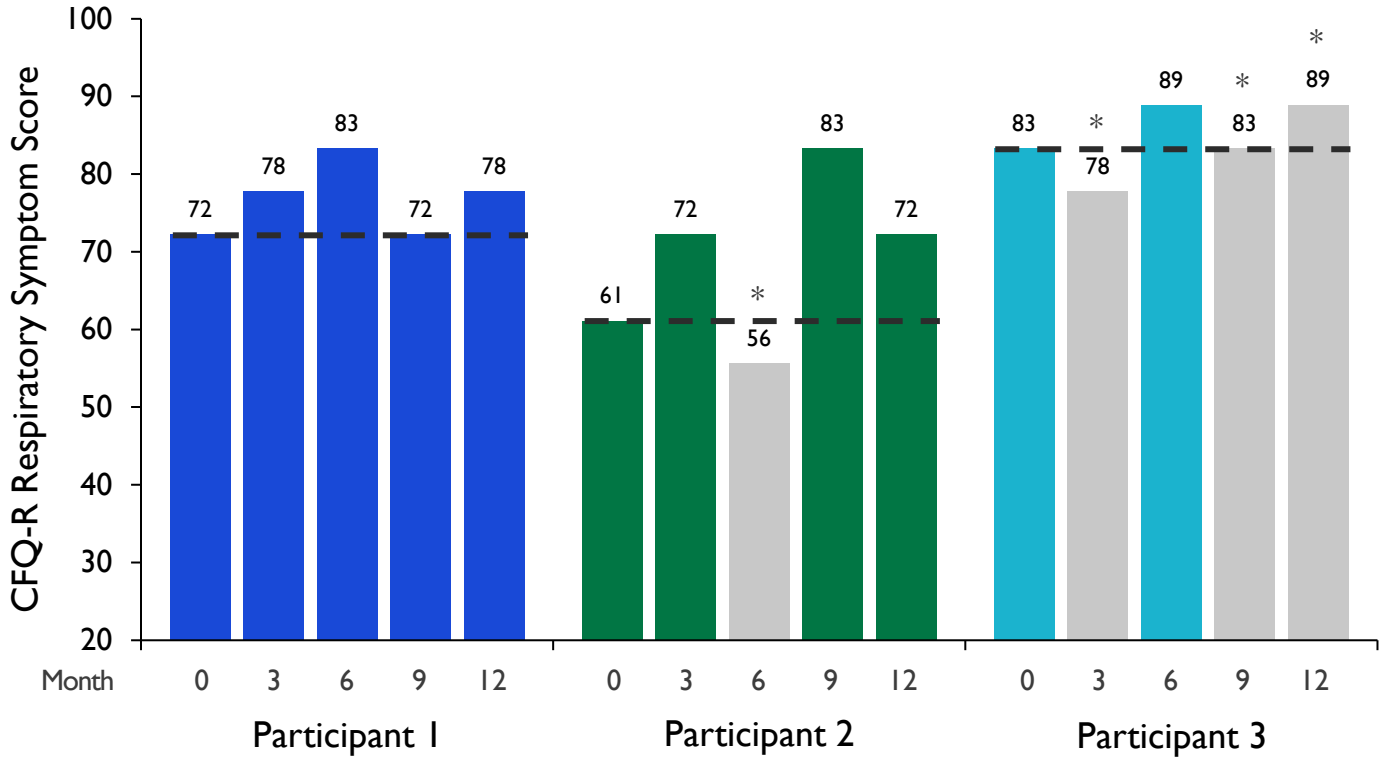
Cohort 1	Month 1	Month 3	Month 6	Month 9	Month 12	Beyond Month 12
Participant 2	Day 8: Grade 3 COVID-19, dyspnea	**none**	Day 176: Grade 1 rhinovirus	**none**	**none**	**none** (through month 14)

*Pre-dose spirometry assessment. ppFEV1, percent predicted forced expiratory volume in 1 second. †Within 21 days of assessment.

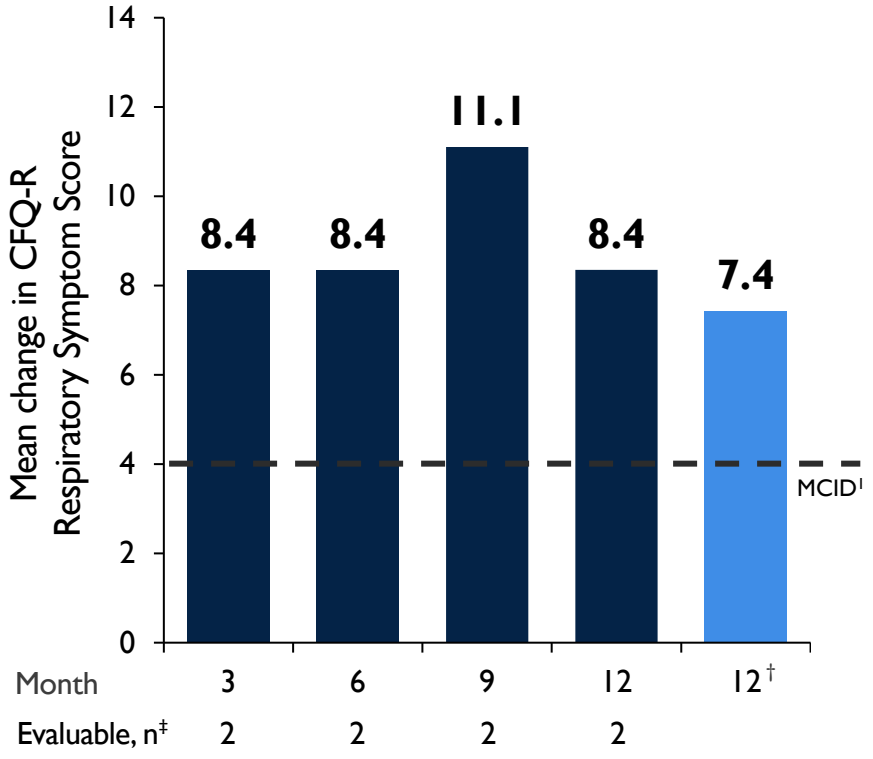
Cohort 1: Durable Improvement in CFQ-R-RD Quality of Life in All 3 Participants

Mean Increase of 8.4–11.1 Points Over 12 Months Consistently Above MCID

CFQ-R Respiratory Symptom Score



Mean Change in CFQ-R Score



*Respiratory-related adverse event within 21 days of assessment. †All enrolled participants (n=3). ‡Excludes participants with a respiratory-related event within 21 days of assessment. CFQ-R-R, Cystic Fibrosis Questionnaire-Revised (respiratory symptoms scale). Scores range from 0 to 100, with higher scores indicating better health. MCID=4 points [1]. 1. Quittner AL et al. *Chest* 2009;135:1610–18.

Cohort 1: Improved and/or Stable Clinical Activity Endpoints Compared to Expected Decline in Historical Data

Assessment	Instrument	Historical Data	4D-710 Outcomes Through 12 Months (n=3)
Spirometry	% Predicted FEV_1	Annual rate of decline: **-1 to -2.3%**[1*,2] Within-subject variability: **SD ±4.5%**[3]	**BL Moderate: Improved (+5-7%)** BL Mild: Stable (0%) BL Normal: Stable (-2%) †
Health-related Quality of Life: Respiratory Symptoms	Cystic Fibrosis Questionnaire-Revised Resp. Domain (CFQ-R-RD)	48 week change from baseline: **Est. -4 points** placebo[4] **MCID**: 4 points[5]	**Clinically meaningful improvement** (≥4 points; MCID): ▪ **3 of 3 participants** ▪ **Mean Increase of 8.4–11.1** and up to **+22 points**

*Estimate based on *DF508* homozygous population, which appears to have a similar rate of decline as Class I (null) variant population. †Based on last evaluable time point.
CFQ-R-R, Cystic Fibrosis Questionnaire-Revised (respiratory symptoms scale); MCID, minimal clinically important difference; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; QoL, quality of life; SD, standard deviation.
1. Konstan MW et al. *Lancet Respir Med* 2017; 5:107–18. 2. Caley et al. Journal of Cystic Fibrosis 2021;20:86–90. 3. Stanbrook MB et al. *Chest* 2004; 125:150–5. 4. Ramsey et al. *N Engl J Med* 2011; 365:1663–72. 5. Quittner AL et al. Chest 2009;135:1610–18.

Strong Clinical POC Further Advances 4D-710 Program

- **Phase I Dose exploration continues** (2.5E14 – 2E15 vg): expression profile enables lower doses to study gene expression dose response; participants have been dosed in Cohort 3 (n=1) & Cohort 4 (n=1)
- Amendment to AEROW submitted to the Cystic Fibrosis Therapeutics Development Network (TDN):
  1. Enroll pwCF with lower baseline ppFEV$_1$ (50-90%)
  2. Introduce 2nd lung biopsy procedure at 12 months or later
- **Phase I Dose Exploration interim data update** and **dose selection** for Phase 2 Expansion Cohort (anticipate enrolling n=6-9) **at ECFS (June 5-8, 2024)**
- Initial GMP-ready suspension manufacturing process **completed in-house at 500-liter scale**; technology transfer initiation to commercial CDMO anticipated H1 2025

pwCF = people with cystic fibrosis; CFQ-R-RD: Cystic Fibrosis Questionnaire Revised Respiratory Domain

Preliminary Registration Path for 4D-710 for Treatment of People with CF Who are Modulator-Ineligible/-Intolerant

Preliminary Phase 3 Design	
N=	~60-80
Population	pwCF with low baseline $ppFEV_1$ (planned ~40-80%)
Design	Randomized, placebo-controlled (with opportunity for cross-over)
Endpoints	Δ in: $ppFEV_1$, quality-of-life (CFQ-R-RD), frequency of pulmonary exacerbations

Accelerated Approval

Additional FDA/EMA discussions to follow additional AEROW clinical and lung biomarker data in pwCF with low baseline $ppFEV_1$ (50-90%) to evaluate correlation between clinical and biomarker endpoints

Initiation planned in **H2 2025**

pwCF = people with cystic fibrosis; CFQ-R-RD: Cystic Fibrosis Questionnaire Revised Respiratory Domain

Pulmonology Pipeline Key Expected Milestones

VECTOR DELIVERY	PRODUCT CANDIDATE	INDICATION	EPIDEMIOLOGY (PREVALENCE)	RESEARCH CANDIDATE	IND-ENABLING	PHASE 1/2	PHASE 3	EXPECTED UPCOMING MILESTONES
PULMONOLOGY **AAT** **Aerosol** 	4D-710	Cystic Fibrosis Lung Disease (modulator ineligible / intolerant)	*~15K WW*			AEROW		▪ **June 5-8, 2024** Interim update from Phase 1/2 AEROW clinical trial, and Phase 2 Expansion Cohort dose selection at ECFS ▪ **H2 2025** Pivotal trial initiation
		Cystic Fibrosis Lung Disease (combo with modulators)	*~90K WW*					▪ **June 5-8, 2024** Development plan for patients on modulators during ECFS update
	4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EUMM*					▪ **2024** Program update

4DMT

CARDIOLOGY 

Vector: C102

- **4D-310:** Fabry Disease Cardiomyopathy

C102 & 4D-310 Designed for Low Dose IV Delivery to the Heart

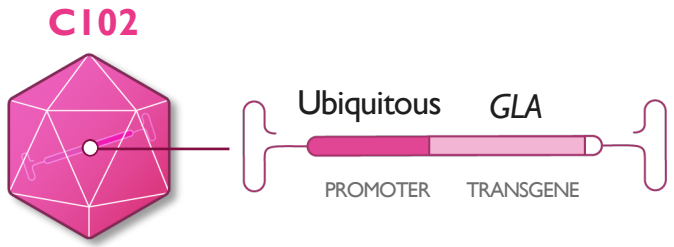
Cardiac disease is the most common cause of death (75%)[1] in Fabry disease

Current therapies do not adequately address Fabry-related cardiovascular manifestations[2–5]

- ✕ ERT does not improve cardiac function[6]
- ✕ Nominal effect on exercise capacity with migalastat in patients with amenable GLA variants[7] (~35% of patients)[8]
- ✕ No therapy has been shown to clear accumulated Gb3 from cardiomyocytes
- ▪ **Significant unmet medical need**

Intravenous C102-Based Genetic Medicines

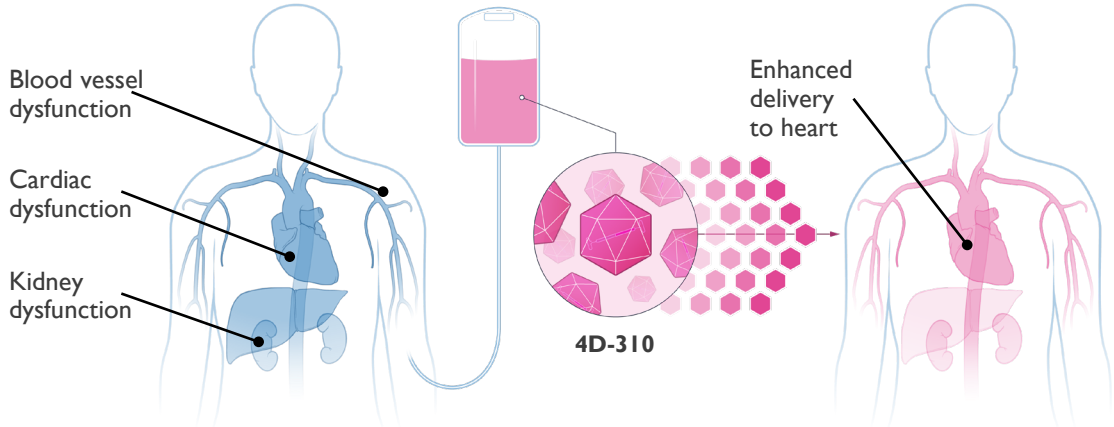
4D-310



Vector: C102 (**cardiac targeting** evolved AAV)

Transgene: *GLA* (encodes AGA enzyme)

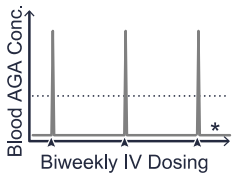
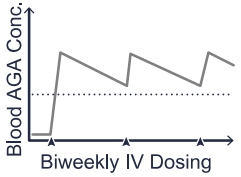
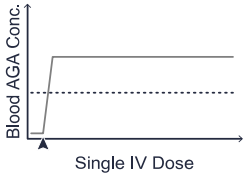
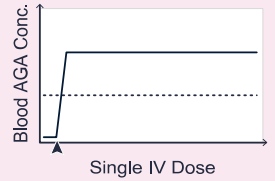
Promoter: Ubiquitous



AGA, a-galactosidase A; Gb3, globotriaosylceramide; AAV, adeno-associated virus.

1. Baig S et al. Europace 2018;20:153–61. 2. Waldek S et al. Genet Med 2009;11:790–796. 3. Banikazemi M et al. Ann Intern Med 2007;14:77–86. 4. Tsukimura T et al. Mol Genet Metab Rep 2020;25:100650. 5. Azevedo O et al. Int J Mol Sci 2021;22:4434. 6. Lobo T et al. Intern Med J 2008;38:407–14. 7. Camporeale A et al. J Med Genet 2023;60:850–8. 8. Hughes et al. J Med Genet. 2017;54:288–96.

4D-310 Unique MOA Well-Differentiated Versus ERT & Genetic Medicines for Fabry Disease Cardiomyopathy

		ERT (Blood)		Genetic Medicine	
MOA	**Product Design**	AGA Enzyme Infusions	PEGylated AGA	AAV-mediated Liver-directed	**4D-310**
AGA Delivery Through the Bloodstream	Pharmacokinetics (··· Normal; ▲ Time of dose; * Lifelong)				
	Single dose administration	–	–	+	+
	Liver secretion of AGA	–	–	+	+
Cardiovascular Treatment & AGA Production in Target Cells	Heart (cardiomyocytes)	–	–	–	+
	Kidney (glomeruli, including podocytes)	–	–	–	+
	Blood vessels	–	–	–	+
Antibody Resistance	Intracellular production in target tissues (anti-AGA antibody avoidance)	–	–	–	+
	Capsid evolved for resistance to preexisting NAb	–	–	–	+

Abbreviations: Ab, antibodies; AGA, aspartylglucosaminidase; AAV, adeno-associated virus; ERT, enzyme replacement therapy; IV, intravenous.

Phase 1/2 Open Label Clinical Trials: 4D-310 for Fabry Disease Cardiomyopathy

	INGLAXA-1	INGLAXA-2
Geography	U.S. multicenter *(Currently on Clinical Hold)*	Taiwan & Australia multicenter
Patient Population	Male or female adults; classic or late onset Fabry disease; cardiac involvement* (on or off ERT)	
4D-310 Dose	**1E13 vg/kg** IV infusion	
Immune Regimen	**Amending to rituximab & sirolimus (R/S)**	
Primary Endpoint	Safety	
Secondary Endpoints	**Cardiac imaging, function, QoL status**	
Cardiac Biopsy Endpoints	n.a.	**Transgene delivery, RNA expression & AGA protein expression**
C102 NAb Screening	Exclude high titer NAb to C102 (>1:1,000)	
AGA Ab Screening	Exclude high titer antibodies to AGA (≥1:25,000)	

*Eligibility for INGLAXA-2 required evidence of left ventricular hypertrophy on ECHO or CMR within 12 months prior to screening. AGA, a-galactosidase A; ERT, enzyme replacement therapy; NAb, neutralizing antibody.

Cardiac Assessments: Multiple Diverse Endpoints

Study Assessment	Method	Time Points
Transgene delivery & expression, Gb3 accumulation *Exploratory endpoint* (INGLAXA 2)	Cardiac Biopsy*	Weeks 6, 26
Cardiac contractility (global longitudinal strain) *FDA-recommended supportive endpoint*	Echocardiogram†	Months 6, 9, 12, 18, 24
Exercise capacity (peak VO_2) *FDA-recommended primary endpoint*	CPET†	Months 6, 9, 12, 18, 24
Cardiac quality of life (physical limitations, symptoms) *FDA-recommended primary endpoint*	KCCQ	Months 6, 9, 12, 18, 24

*Transgene delivery assessed by qPCR; transgene RNA expression analyzed by RT-qPCR and *in situ* hybridization; AGA protein evaluated by immunohistochemistry; Gb3 accumulation in cardiomyocytes evaluated by electron microscopy and image analysis.
†Assessed by independent central reading center.
CPET, cardiopulmonary exercise test; KCCQ, Kansas City Cardiomyopathy Questionnaire; MRI, magnetic resonance imaging.

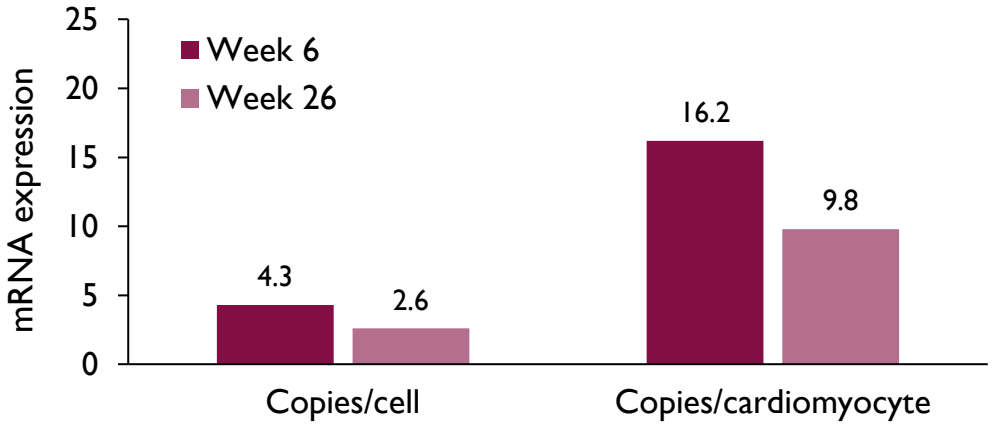
Baseline Patient Characteristics

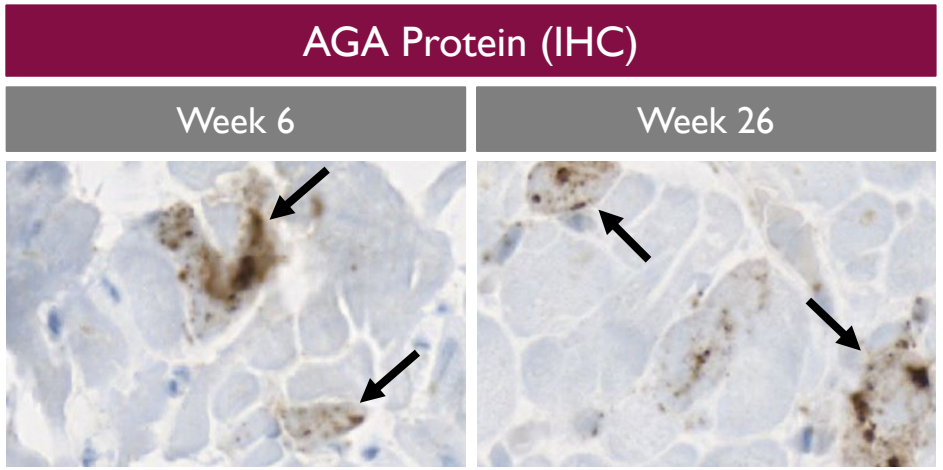
	INGLAXA 1				INGLAXA 2	
Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Disease classification	Classic	Classic	Classic	Late onset	Late onset	Late onset
GLA variant	c.1023A>C	c.708G>T	c.974G>A	c.671A>G	IVS4+919 G>A	c.644 A>G
Serum AGA activity, nmol/hr/mL*	0.42	0.00	0.30	0.06	1.62	0.18
Serum lyso-Gb3, ng/mL†	6.28	101.0	8.78	45.0	3.79	3.2
ERT experience	Yes	Yes	Yes	No	Yes	Yes
ERT status at enrollment	On	Off	On	Naïve¶	On	Off¶
Anti-AGA antibody titer	1:947	1:99,900	1:13,900	Negative	Negative	Negative
Peak VO_2, % predicted	na	33.0	66.1	30.3	76.0	120.2
Global longitudinal strain, %	**–17.10**	–22.17	**–18.83**	–23.27	–21.95	–20.63
Left ventricular mass index, g/m^2	86.7	81.8	67.8	73.1	58.4	105.9

*Reference range, 4.44–27.42 nmol/hr/mL. †Reference range, ≤1.0 ng/mL. ‡Reference range, >60 mL/min/1.73m^2. ¶On migalastat at enrollment. LVMI normal range, 49–85 g/m^2.
AGA, α-galactosidase A; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; Gb3, globotriaosylceramide; NR, not reported.

Cardiac Biopsy: Robust & Durable Transgene Expression in Cardiomyocytes

- Single participant with repeated cardiac biopsy (Weeks 6 & 26)*
- No inflammation
- Paired analysis of biopsies demonstrated **widespread** transduction & **durable** transgene expression
  - Genome delivery (qPCR)
  - RNA expression (ISH, RT-qPCR)
  - AGA protein (IHC)
- 4D-310 transgene expression observed predominantly in cardiomyocytes

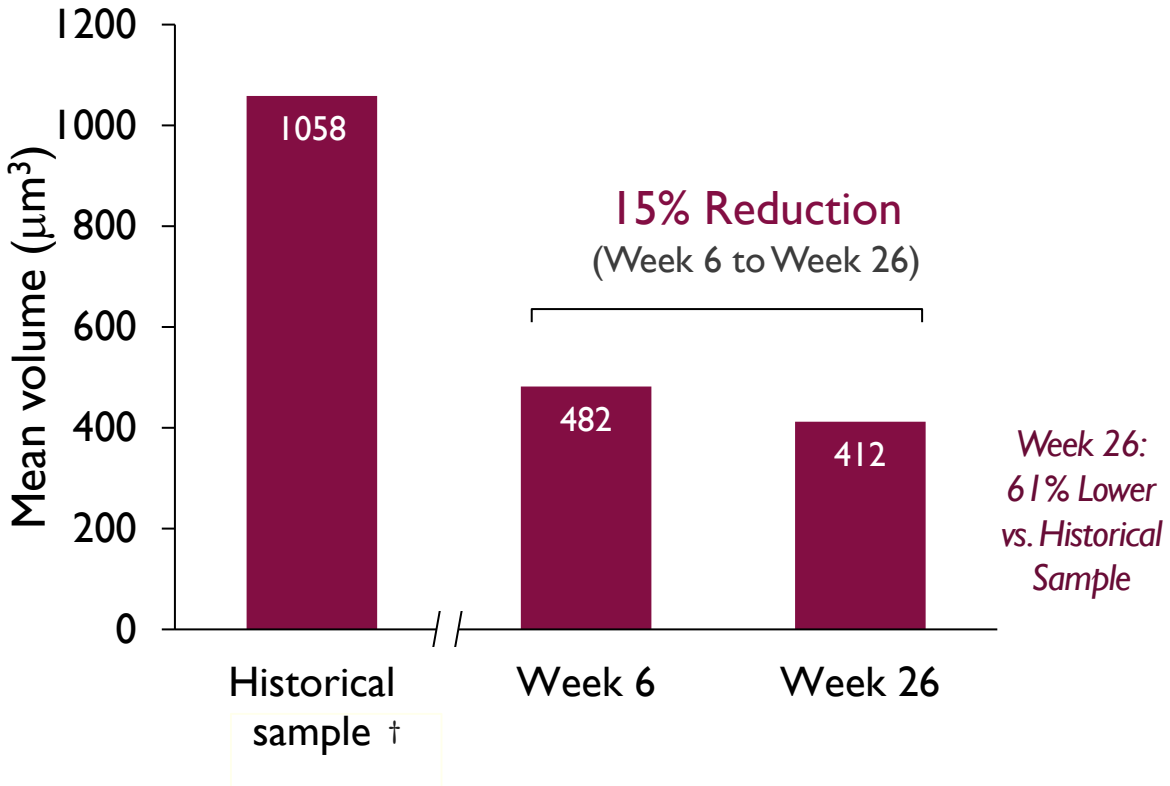




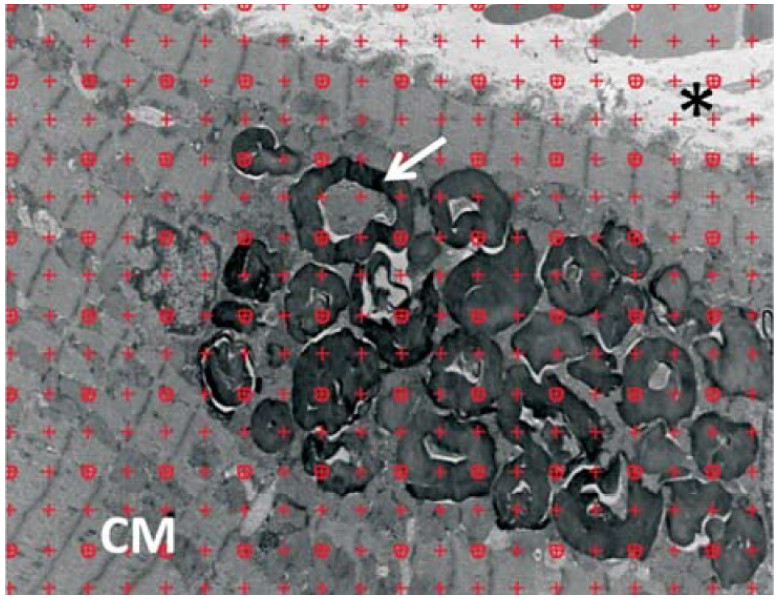
*Male (57 y) with late-onset Fabry disease. †Calculated based on an estimated 30% ratio of cardiomyocytes to total heart cells. IHC, immunohistochemistry; ISH, *in situ* hybridization; qPCR, quantitative polymerase chain reaction; RT-qPCR, reverse transcription-qPCR.

Cardiac Biopsy: Reduction in Gb3 Substrate Accumulation in Cardiomyocytes

Mean Gb3 Inclusion Body Volume per Cardiomyocyte



Ultra-high resolution electron microscopy & image analysis used to identify cardiomyocytes & quantify the volume of Gb3 inclusions[1]



Point grid superimposed on cardiomyocytes for estimation of Gb3 inclusion volume. White arrow, Gb3 inclusion; asterisk, interstitium [1].

***No approved therapy** has been shown to clear accumulated Gb3 from cardiomyocytes in Fabry disease patients*

*Male (57 yr) with late-onset FD (IVS4+919G>A). †Sample collected prior to enrollment and analyzed independently by investigator [1]. 1. Chang et al. 2023.12.09.23298489; doi: https://doi.org/10.1101/2023.12.09.23298489.

Global Longitudinal Strain: Ventricular Function Improved or Stable in All Evaluable Participants

Patient	Baseline (Screening)		Change from Baseline (%)		
			Month 6	Month 12	Month 24
1	–17.10	Borderline	–1.1	**–2.5**	**–2.9**
3	–18.83	Low normal	–0.5	**–3.3**	**–2.8**
2*	–22.17	Normal	na	–1.1	na
5	–21.95‡	Normal	na¶	–1.2‡	
6	–20.63	Normal	–0.4	–0.3	
Historical ERT†	–13.2			**+1.1**	–

MCID=1.5%[2]

GLS was measured in 3 apical views (4-, 3- and 2-chamber); the average value is shown.
GLS range (borderline), –16.0 to –18.0% [1]; Minimal detectable difference, 1.5% [2].
*High antibody titer, entered study off ERT.
†Mean value, historical control (N=18); median duration of ERT, 4.2 years (range, 1.4–12.2) [3].
‡GLS average of 4- and 2-chamber views (3-chamber view not available)
¶Not evaluable.

1. Yang H et al. *JACC Cardiovasc Imaging* 2018;11:1196–1201. 2. Lambert J et al. *Heart* 2020;106:817–23. 3. Nordin S et al. *Circ Cardiovasc Imaging* 2019:e009430.

Cardiopulmonary Exercise Testing: Durable Improvement in Peak VO_2 in 3 of 4 Evaluable Participants

Patient	Measurement	Baseline	Change from Baseline		
			Month 6	Month 12	Month 24
1	mL/kg/min (% predicted)	na	nc*	**+2.0**† (+6.3)†	**+7.8**† (+24.6)†
2‡	mL/kg/min (% predicted)	14.0 (33.0)	na	**+7.0** (+17.0)	na
3	mL/kg/min (% predicted)	23.0 (66.1)	+0.4 (–0.3)	–2.2 (–7.8)	–4.1 (–15.6)
5	mL/kg/min (% predicted)	24.8 (76.0)	**+2.6** (+9.4)	**+1.8** (+8.3)	
Historical ERT¶	mL/kg/min	24.1		**–1.8**	**–2.3**

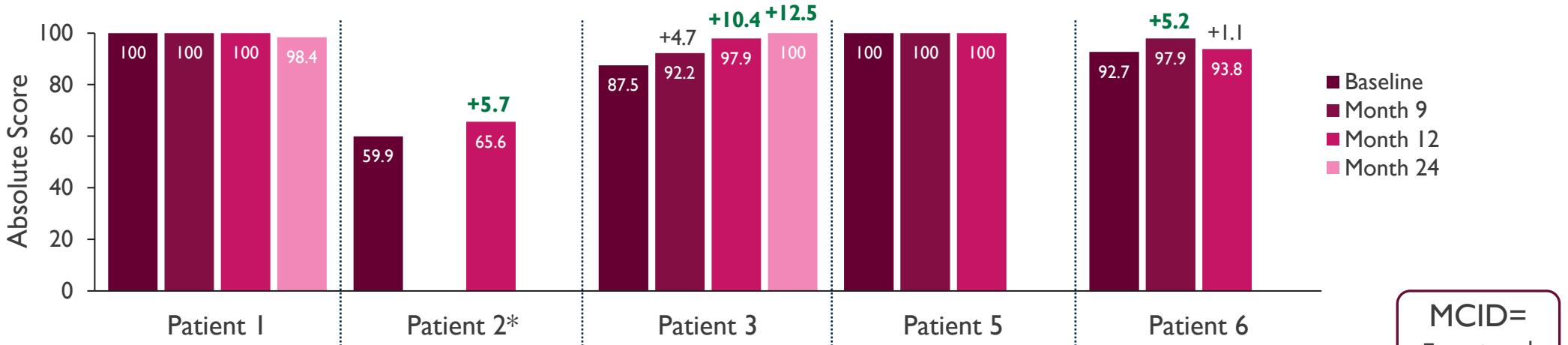
MCID=
1.5 mL/kg/min[1]

Minimal clinically important difference, 1.5 mL/kg/min [1].
*Not calculable (missing baseline data).
†Calculated as change from Month 6 values (21.4 mL/kg/min, 72% predicted).
‡High antibody titer, entered study off ERT.
¶Mean value, historical control (N=14); median duration of ERT, 48 months [2].

1. Wilkinson. *Am J Phys Med Rehabil* 2019;98:431. 2. Lobo T et al. *Intern Med J* 2008;38:407–14.

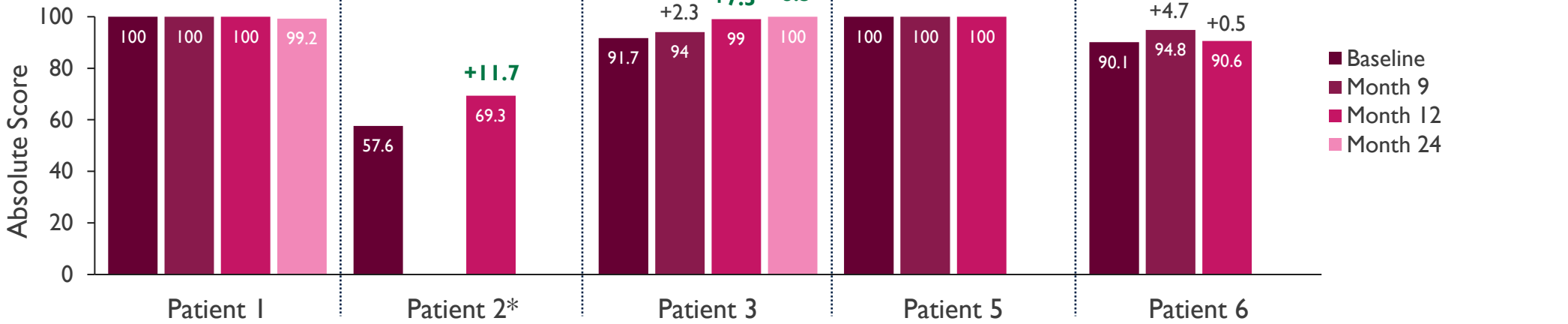
Kansas City Cardiomyopathy Questionnaire (KCCQ): Improved or Stable QoL in All Evaluable Participants

Clinical Summary Score



MCID= 5 points[1]

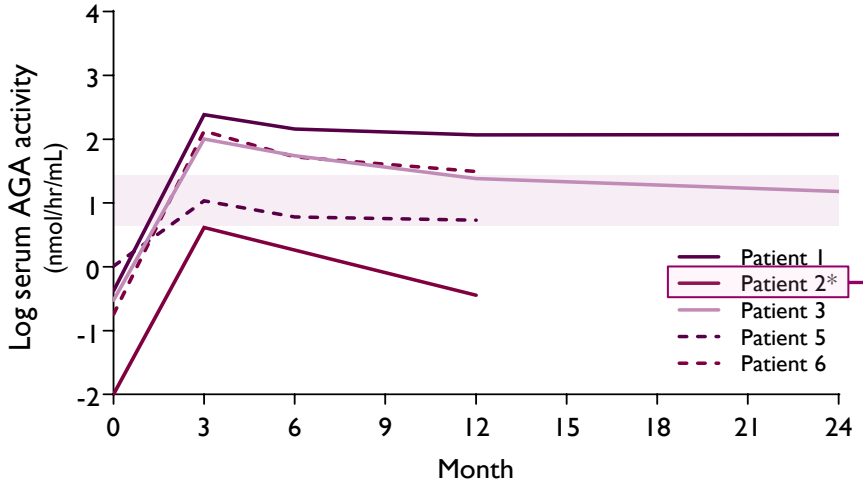
Overall Summary Score



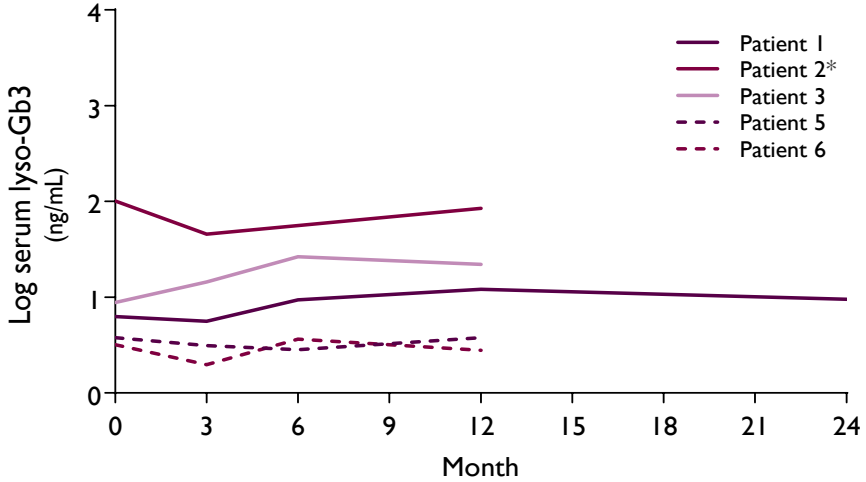
Scores range from 0 to 100 (higher score=less severe); minimal clinically important difference (overall summary score), 5 points [1]. *High antibody titer; entered study off ERT. 1. Spertus JA et al. JACC 2020;76:2379–90.

Considerable Inter- and Intrasubject Variability in Serum Biomarkers, No Correlation with Cardiac Outcomes

Serum AGA Activity



Serum Lyso-Gb3



Cardiac Outcomes (Patient 2)

Outcome	Baseline	Month 12	Change
Peak VO_2 (mL/kg/min)	14.0	21.0	+7.0
Peak VO_2 (% predicted)	33.0	50.0	+17.0
GLS (%)	–22.17	–23.27	–1.1
KCCQ			
Clinical Summary score	59.9	65.6	+5.7
Overall Summary score	57.6	69.3	+11.7

- Consistent with 4D-310 design characteristics, no correlation observed between serum AGA activity and cardiac outcomes

*High antibody titer (1:99,900) at baseline, entered study off ERT. Serum AGA normal range, 4.44–27.42 nmol/hr/mL (depicted as shaded area on graph). Lyso-Gb3 normal range, ≤1.0 ng/mL AGA, α-galactosidase A; Lyso-Gb3, globotriaosylsphingosine.

4D-310 Safety & Next Steps

- 4D-310 was generally well tolerated
  - No clinically significant cardiac or liver toxicities
  - Previously reported cases of aHUS (n=3) fully resolved, no new 4D-310–related AEs > Grade 1
- Alignment with U.S. FDA on plan to lift the clinical hold on U.S. study
  - Protocol amended to change immunosuppressive regimen to rituximab & sirolimus
    - Minimize aHUS risk with IV AAV
  - NHP safety study underway evaluating IV 4D-310 combined with rituximab & sirolimus
  - **FDA submission expected in Q2 2024**

aHUS, atypical hemolytic uremic syndrome; AAV, adeno-associated virus; NHP, non-human primate.

Program Expectations & Cash Position

Strong Cash Balance to Execute Through Key Near-Term Expected Milestones

Large Market Ophthalmology	 4D-150 for **Wet AMD**	Initial interim 24-week analysis for Phase 2 Population Extension cohort (N=32) at ASRS: **July 2024**
		Update on Phase 3 clinical trial design in: **Q3 2024**
		Initiation of first Phase 3 study: **Q1 2025**
	 4D-150 for **DME**	Initial interim 24-week analysis for Phase 2 Dose Confirmation cohort (N=22): **Q4 2024**
	 4D-175 for **GA**	IND filing: **Q2 2024** Phase 1 initiation: **H2 2024**
Pulmonology	 4D-710 for **CF**	Interim Phase 1 update and Phase 2 Expansion Cohort dose selection at ECFS: **June 5-8, 2024** Pivotal trial initiation: **H2 2025**
Cash Balance		**$589M cash as of end Q1 2024; Runway into H1 2027**

4DMT

THANK YOU

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