4DMT

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

Corporate Presentation | July 2024

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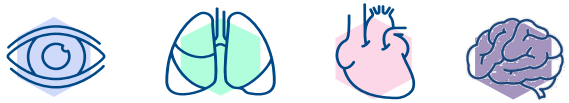
Leading Clinical Stage Next Generation AAV Company

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

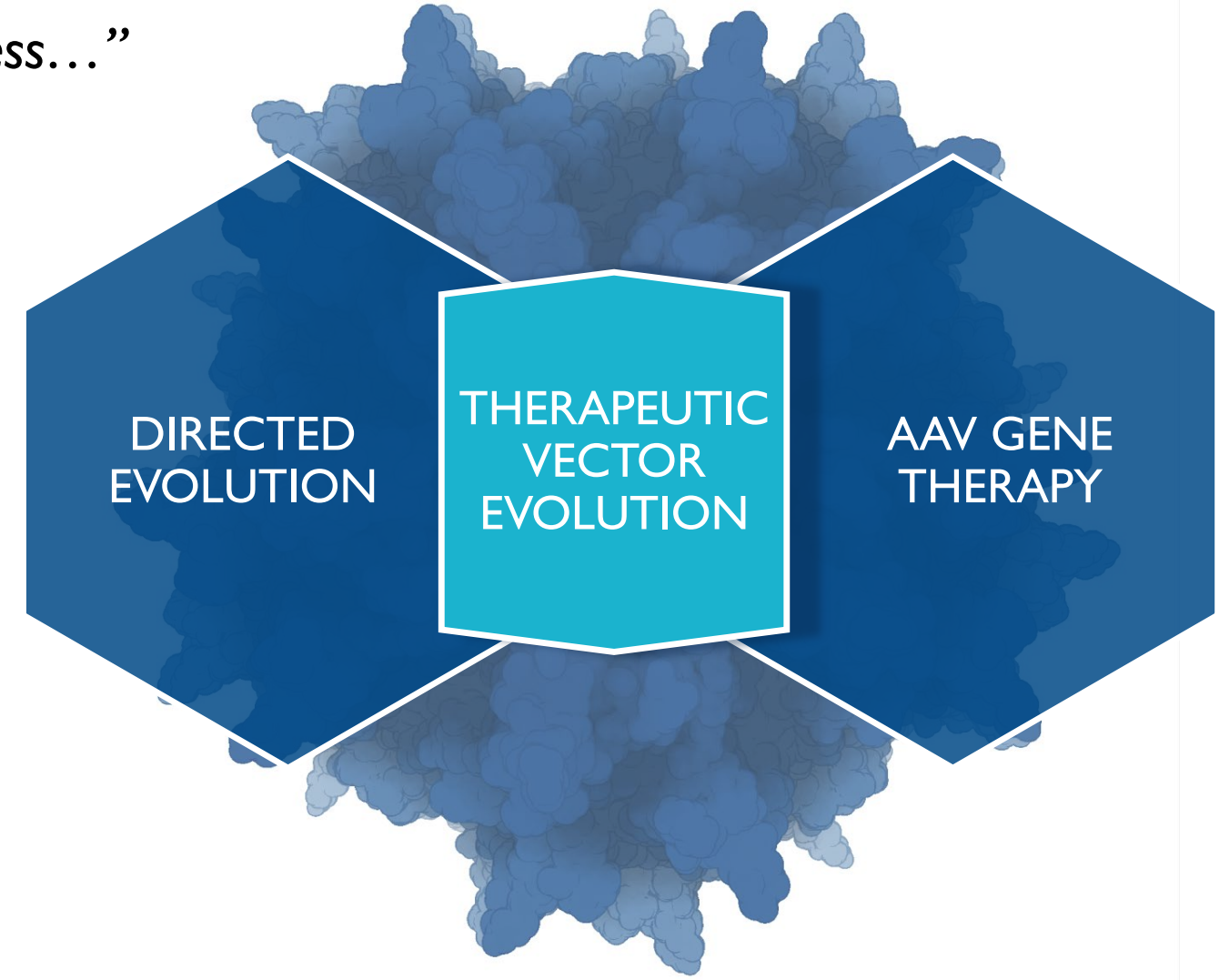
PLATFORM	**DIRECTED EVOLUTION** Nobel Prize-Winning Technology	**~1 BILLION** Proprietary Capsid Sequences	**MODULAR** Customized & Evolved Vectors + Optimized Payloads
PRODUCT ENGINE	**CLINICAL PROOF-OF-CONCEPT**	**4 THERAPEUTIC AREAS** 	**3 ROUTES OF ADMIN** Intravitreal Aerosol Intravenous
PIPELINE		**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

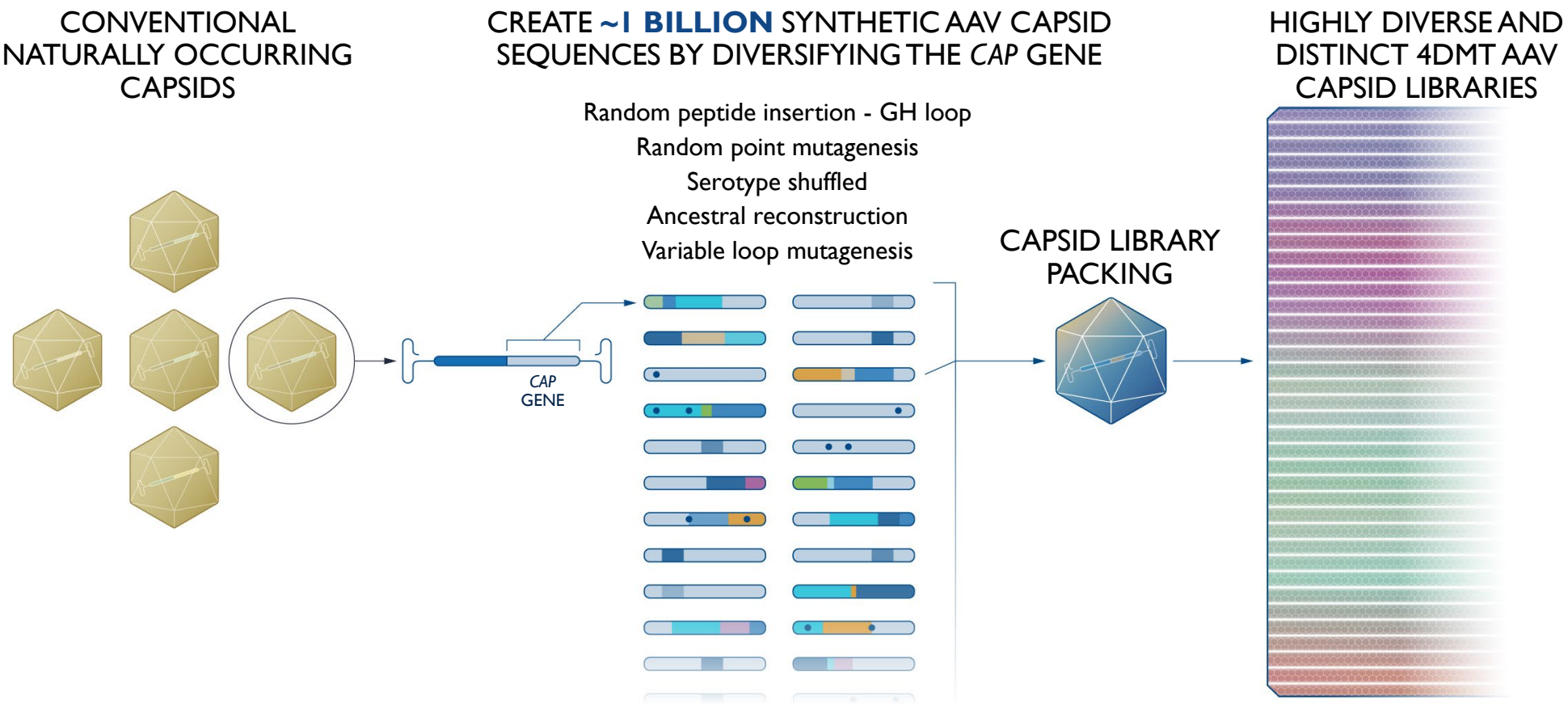
- Limited Delivery
- Limited Transduction
- Increased Inflammation and Toxicity
- Vulnerability to Neutralizing Antibodies

Narrow Focus on Niche Diseases

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

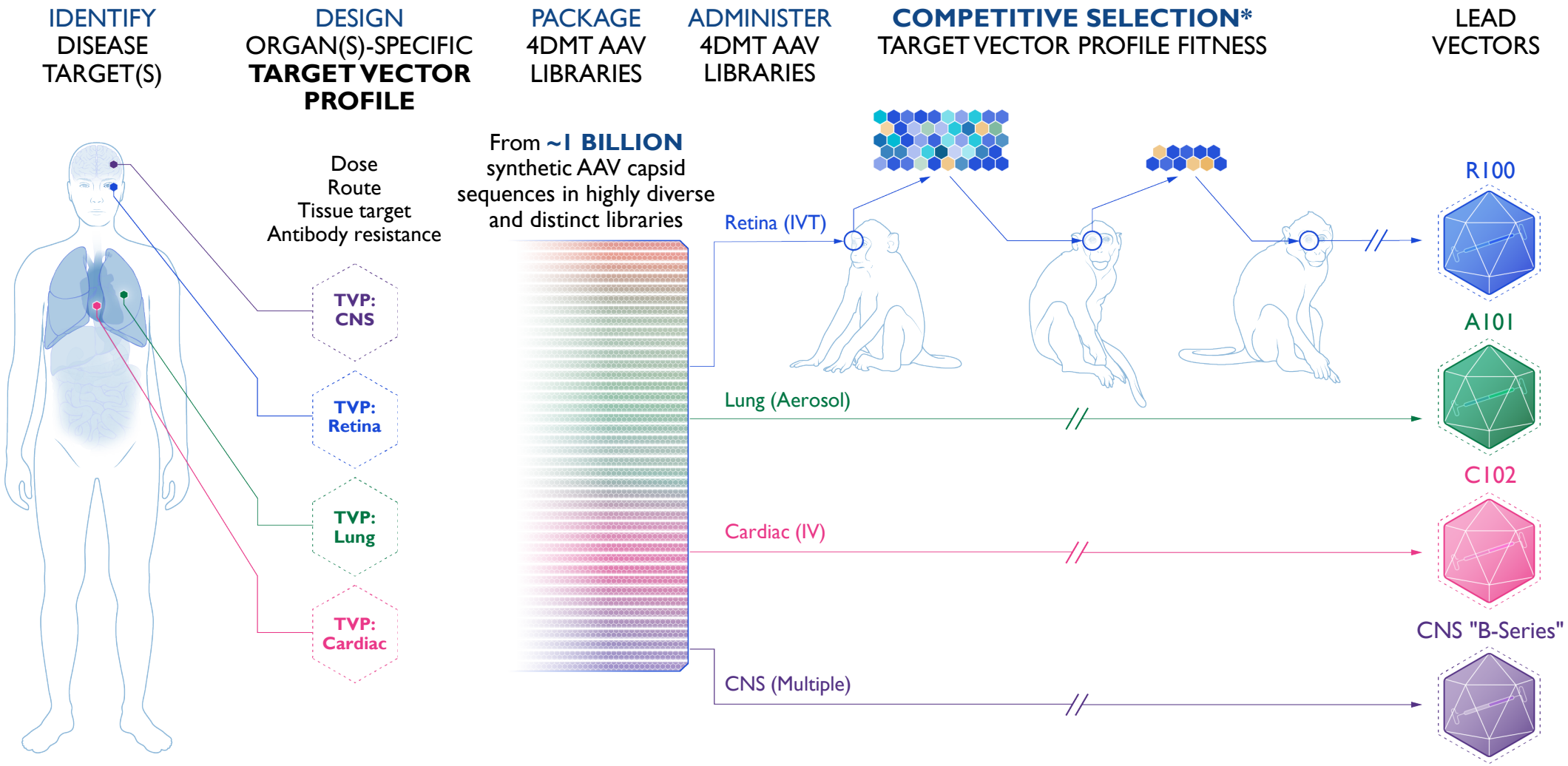
Platform Solution: ~1 Billion Synthetic Capsid Sequences

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 (on-modulator)	~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 and Diabetic Eye Diseases Represent Large Market Retina Opportunities

Large & Growing Worldwide Retinal Disease Market

(Wet AMD, DME, DR & Others)

>$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]

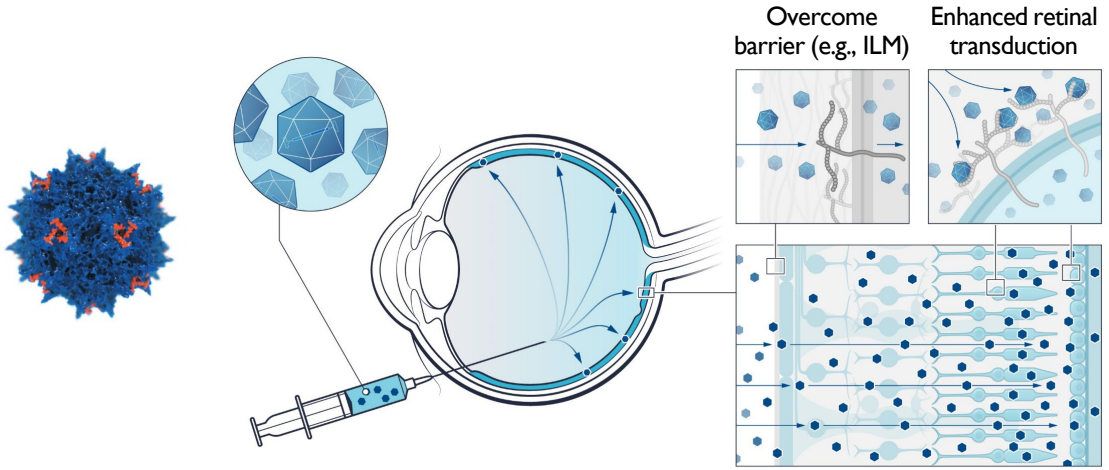
Upregulation of VEGF-C may contribute to treatment resistance[4–6]

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

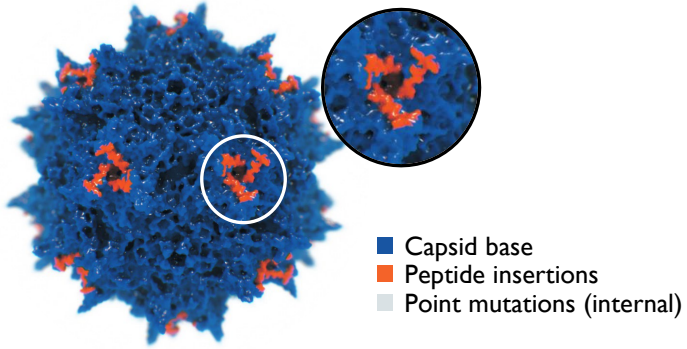
1. 2023 ASRS PAT survey. 2. Guo et al. *Ophthal Res* 2023; 66:406-12. 3. Evans et al. *JAMA Ophtalmol* 2020;138:1043-51. 4. Cabral et al. *Ophthalmol Retina* 2018;2:31-7. 5. Cao et al. *Circ Res* 2004;94:664-70. 6. Pongsachareonnont et al. *Clin Ophthalmol*. 2018;12:1877-85.
CRT, central retinal thickness.

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

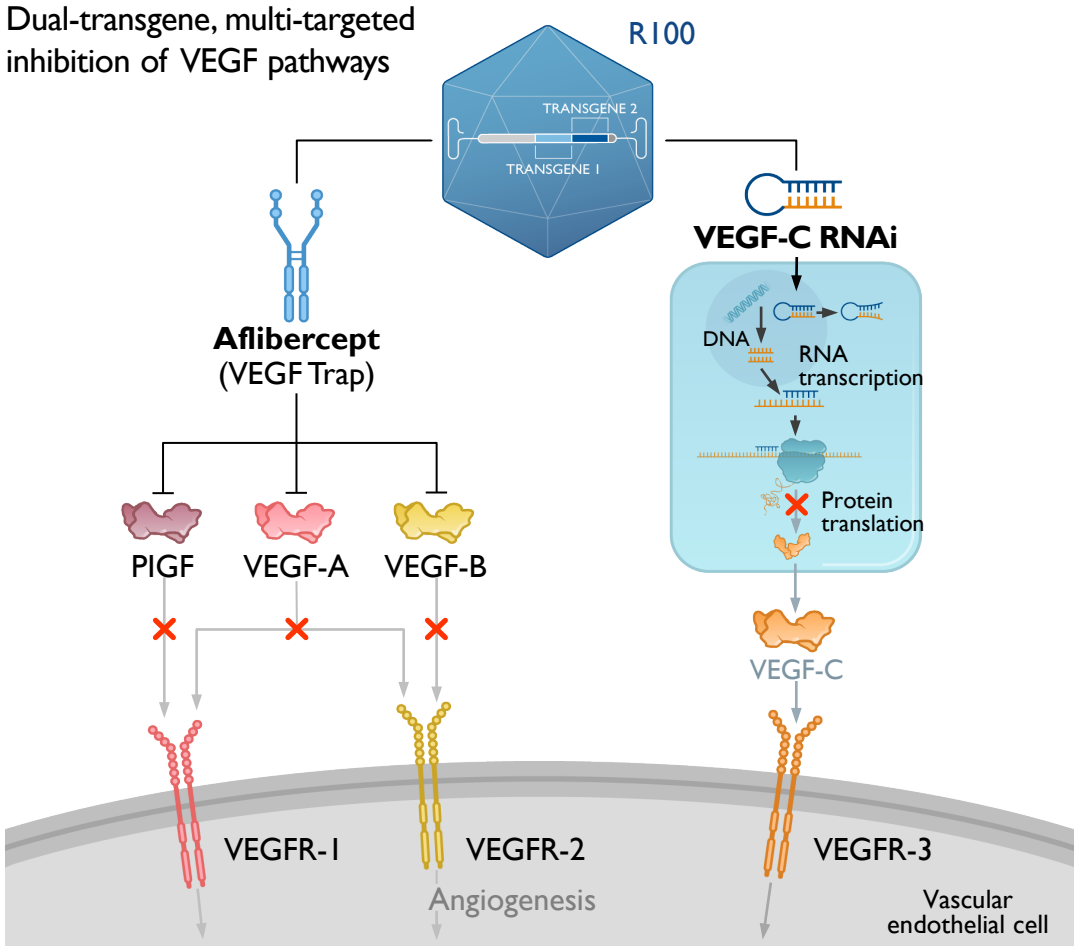
R100



R100 Capsid

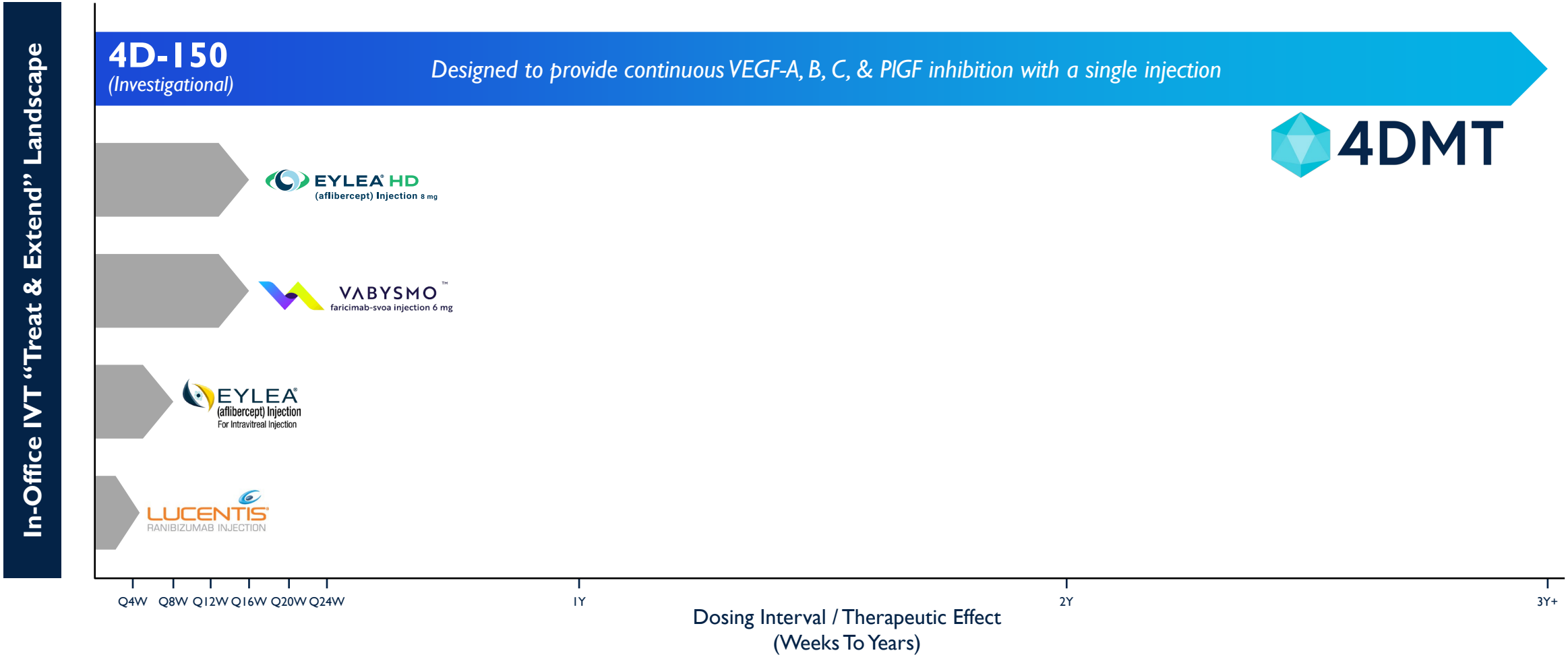


4D-150



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

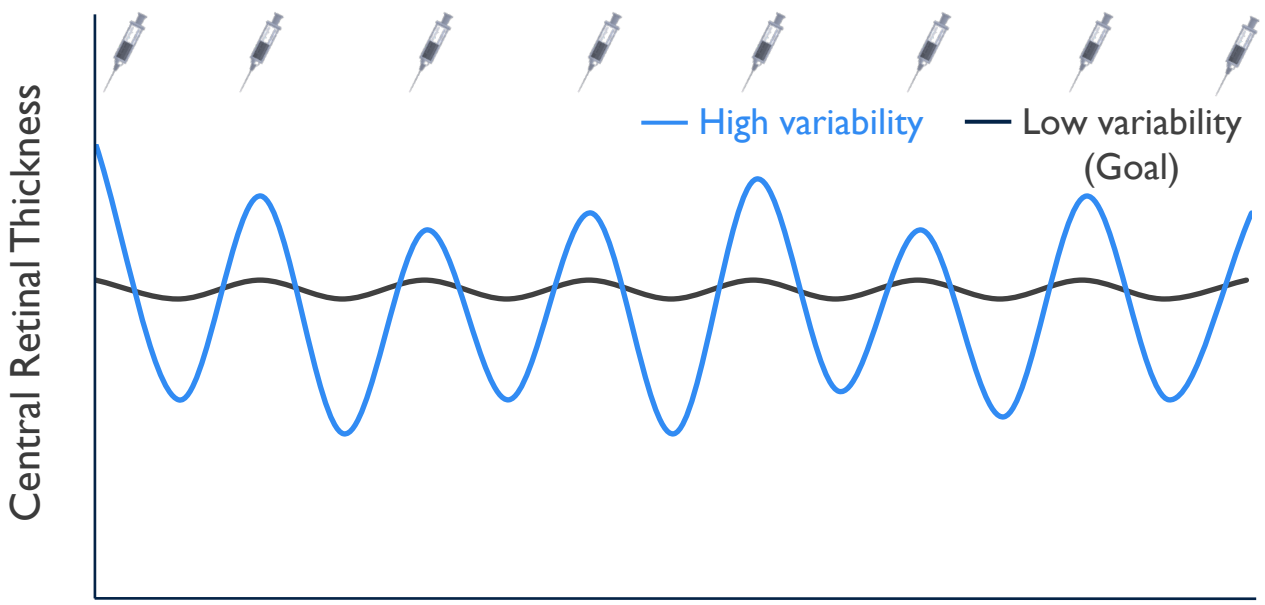
4D-150 Solution: Multi-Year Durability with a Single IVT Injection



FDA labeling.

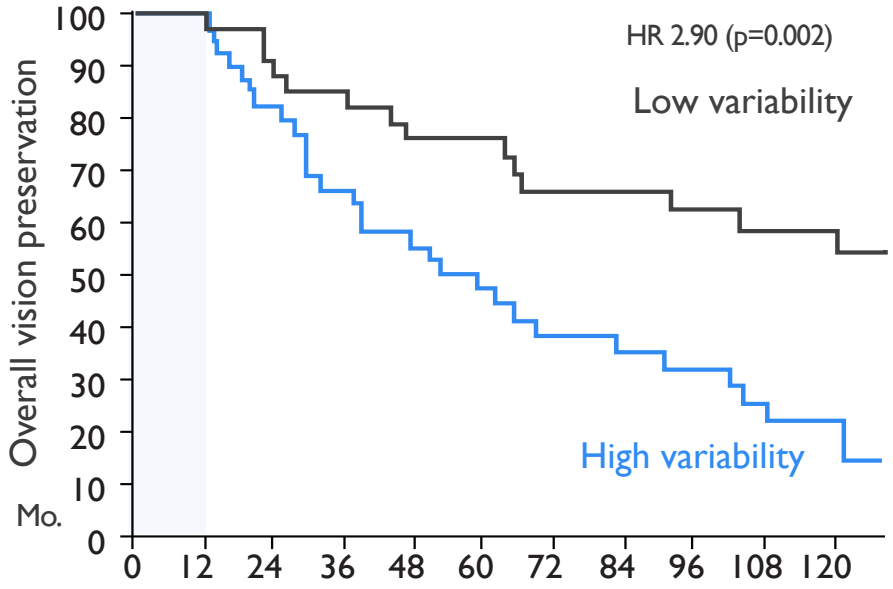
4D-150 Solution: Continuous Retinal Expression of Anti-VEGF to Reduce Retinal Anatomy Variability

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]



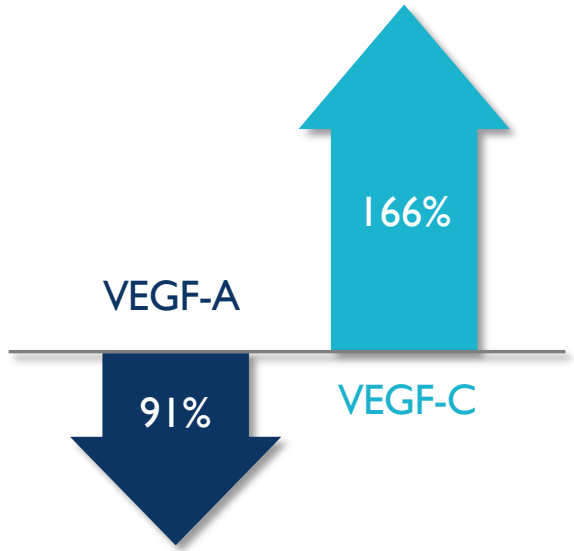
*Higher CRT variability during the first year of treatment is associated with **greater vision loss**[1] & **fibrosis**[2]*

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)

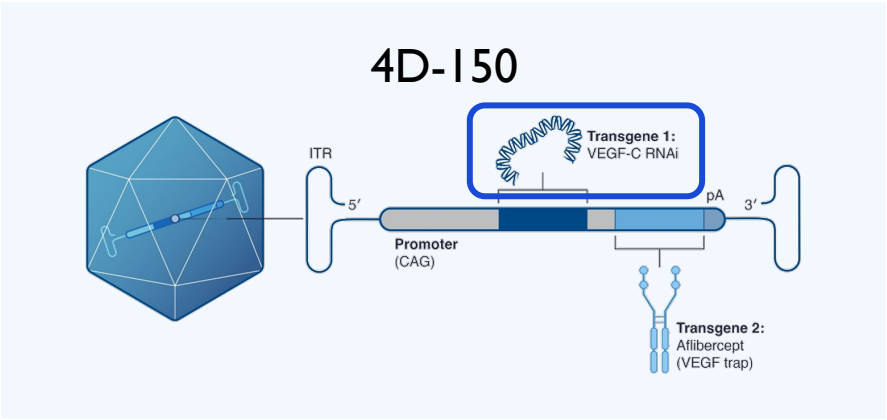
Biological Rationale for Targeting VEGF-C

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

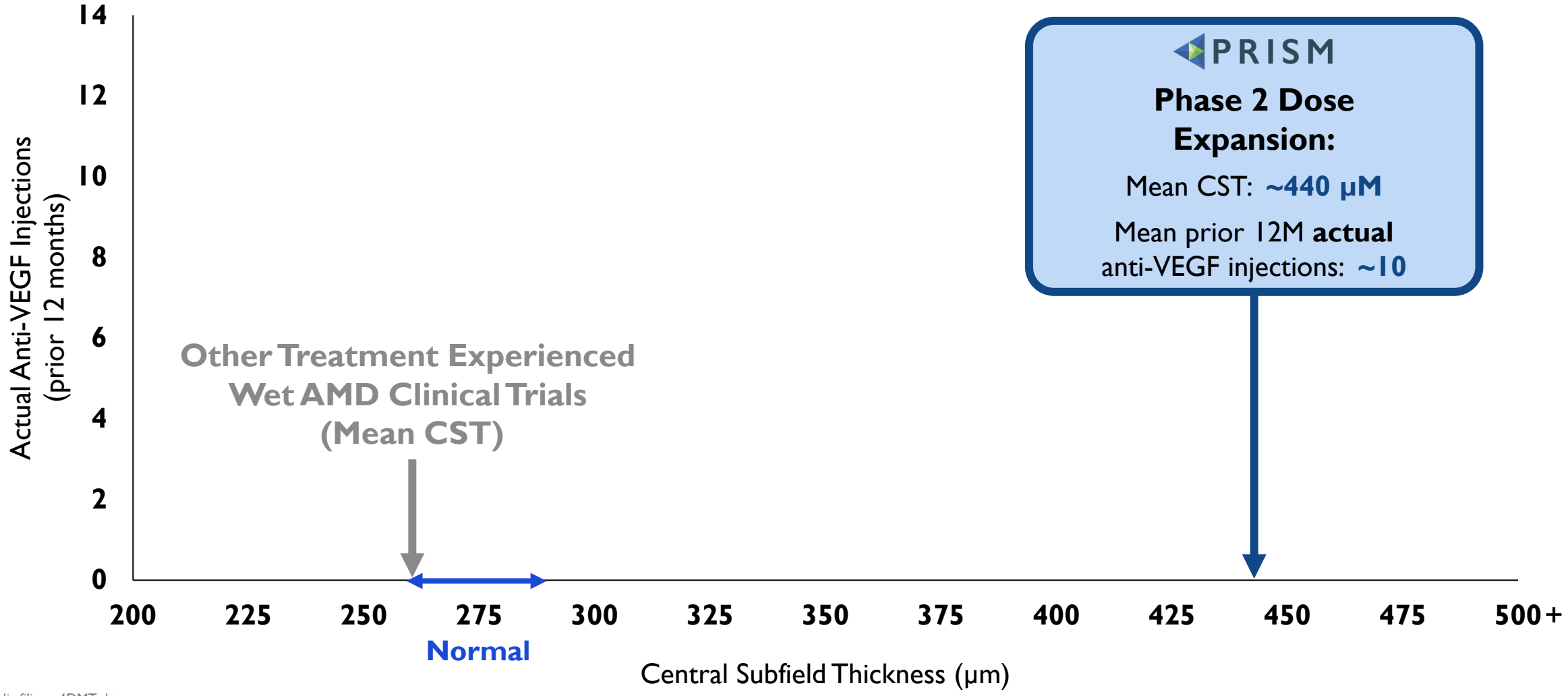
PRISM Phase 2 is Evaluating 4D-150 in a Broad Range of Wet AMD Patient Populations

PRISM

Population:	Severe & High Treatment Burden	Broad Disease Activity
Cohort:	Dose Expansion	Population Extension
	2:2:1 Randomized*: 3E10 vg/eye (n=20); 1E10 vg/eye (n=20); Aflibercept 2 mg (Q8W, n=10)	Sequential: 3E10 vg/eye (n=30); 1E10 vg/eye (n=15)
		24-Week Interim Update Planned at ASRS on July 17, 2024
Key Inclusion Criteria:		
Anti-VEGF Injections in prior 12 months	≥6	**1-6** (≥1 in last 12 weeks)
CST at Screening	≥325 µm AND retinal fluid	**Active disease, with no minimum or maximum CST**
BCVA at Screening	34–83 ETDRS letters	34–83 ETDRS letters

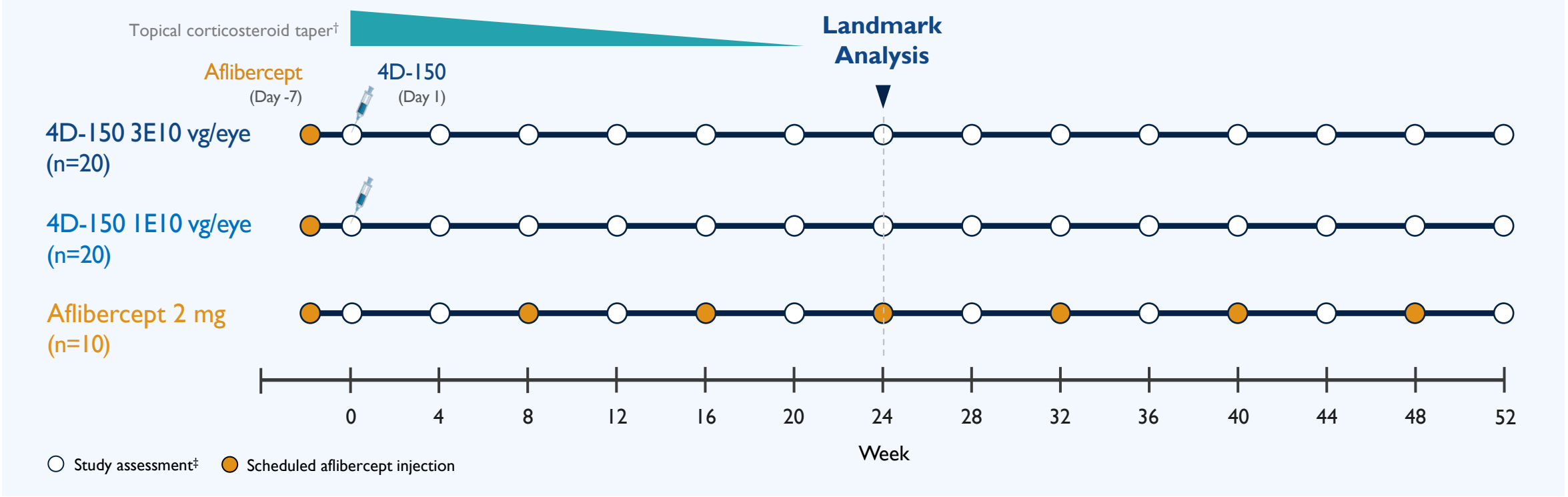
* Stratified by prior injections <9 vs. ≥9. BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

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

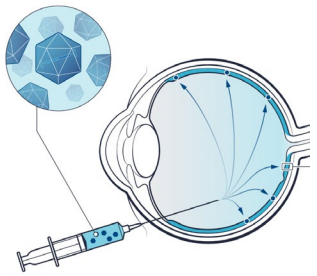
	3E10 vg/eye (n=20)	1E10 vg/eye (n=21)	Aflibercept (n=10)	**Total (N=51)**
Mean ±SD age, years	77 ± 8.0	77 ± 8.6	80 ± 4.1	77 ± 7.7 *(range: 57–92)*
Mean ±SD time since diagnosis, years (% ≥3 years)	4.0 ± 3.0 (60%)	2.9 ± 2.2 (33%)	1.9 ± 1.5 (20%)	3.1 ± 2.5 (41%) *(range: 0.7–11.1)*
Mean ±SD BCVA, ETDRS 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

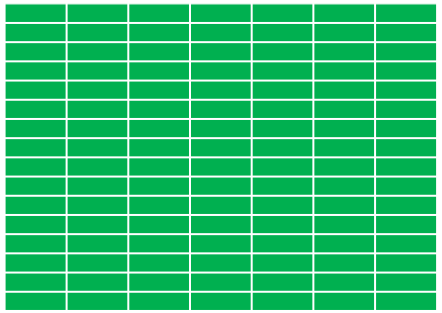
Administration

✓ **Single, routine** intravitreal injection



Safety

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



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

✓ **89%** overall reduction

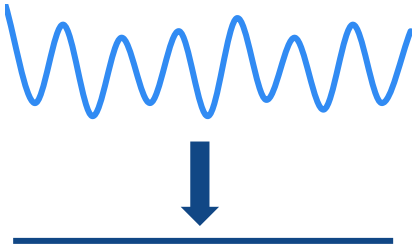
✓ **84%** 0–1 injections

✓ **63%** injection-free

Retinal Anatomical Control

✓ **Improved** retinal anatomical control

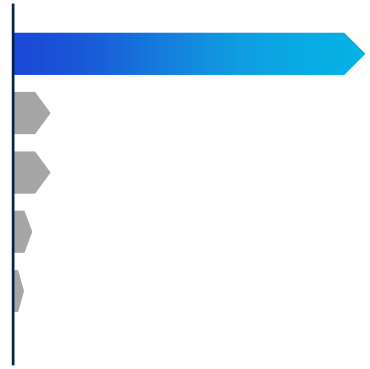
Retinal Thickness



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

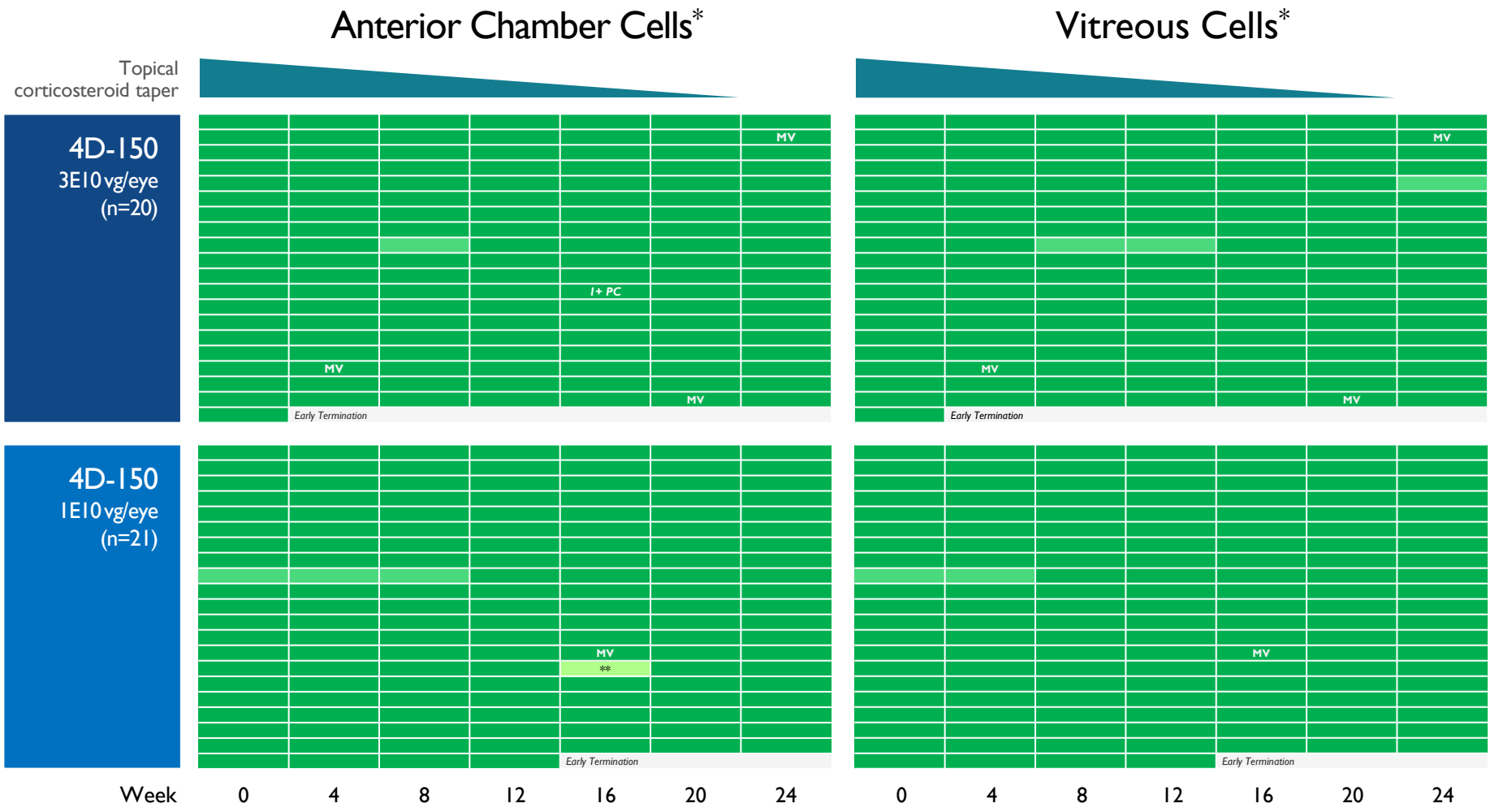
4D-150 Demonstrated Favorable Safety Profile to Date with No Significant or Recurrent Intraocular Inflammation

- **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



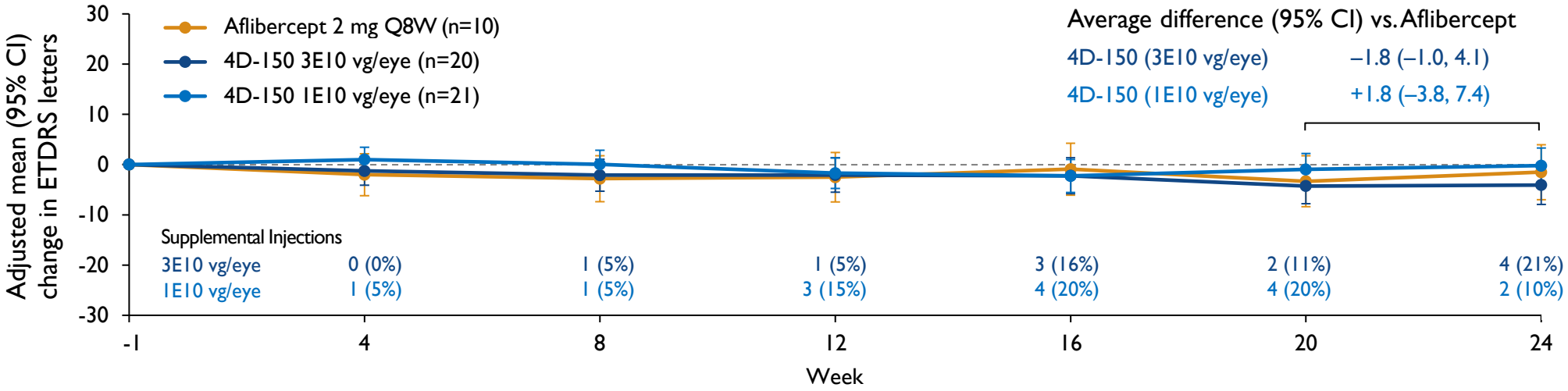
- 97% (38 of 39) completed 20-week corticosteroid taper on schedule
  - Single participant** had an increase in topical corticosteroid, completed taper by week 26
- No patients restarted steroids during follow-up for up to 48 weeks

*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

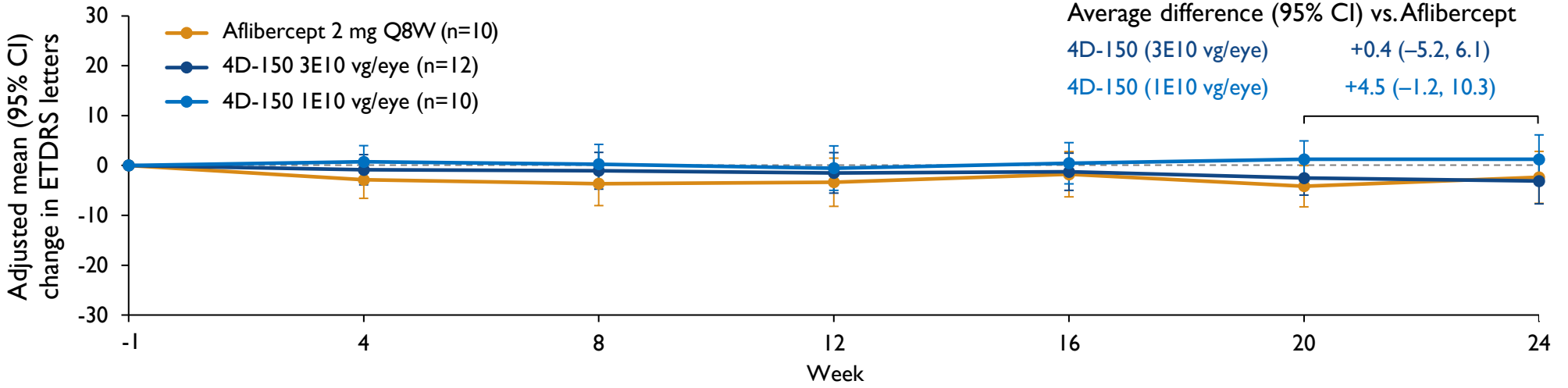
Best Corrected Visual Acuity: Supplemental Injection-free

Stable Visual Acuity Equivalent to Standard Aflibercept Through Week 24 in Injection-free Participants

Total Population
(4D-150, n=41)



Supplemental Injection-free
(4D-150, n=22)

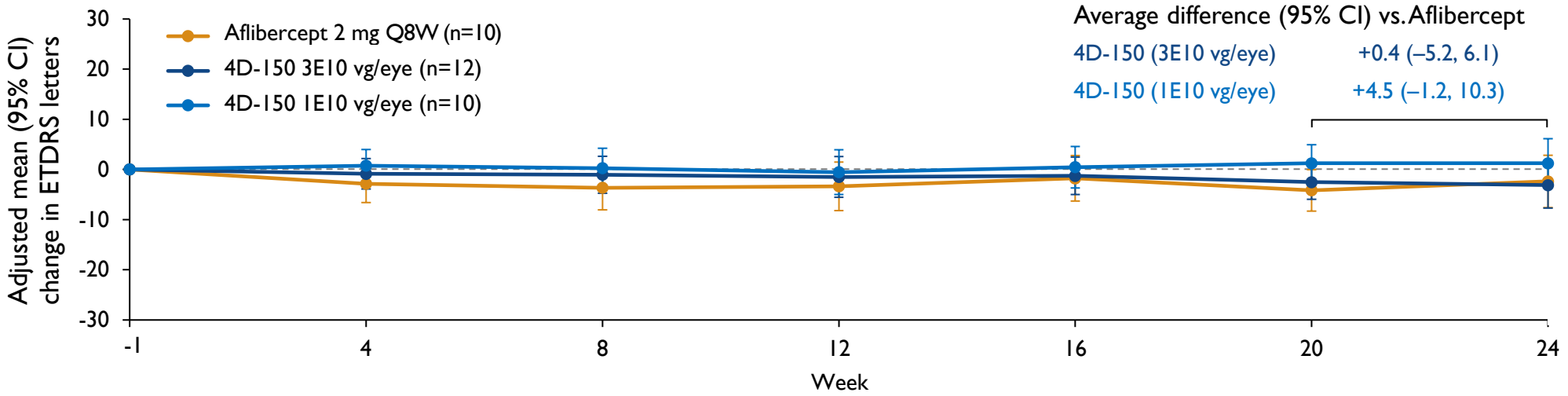


Baseline=Day -7. Adjusted mean (95% CI) estimated from a mixed–effect model for repeated measures (weeks 4-24) without imputation of missing values. Excludes participants (n=1 per dose group) with missing data due to early termination. ETDRS, Early Treatment Diabetic Retinopathy Study.

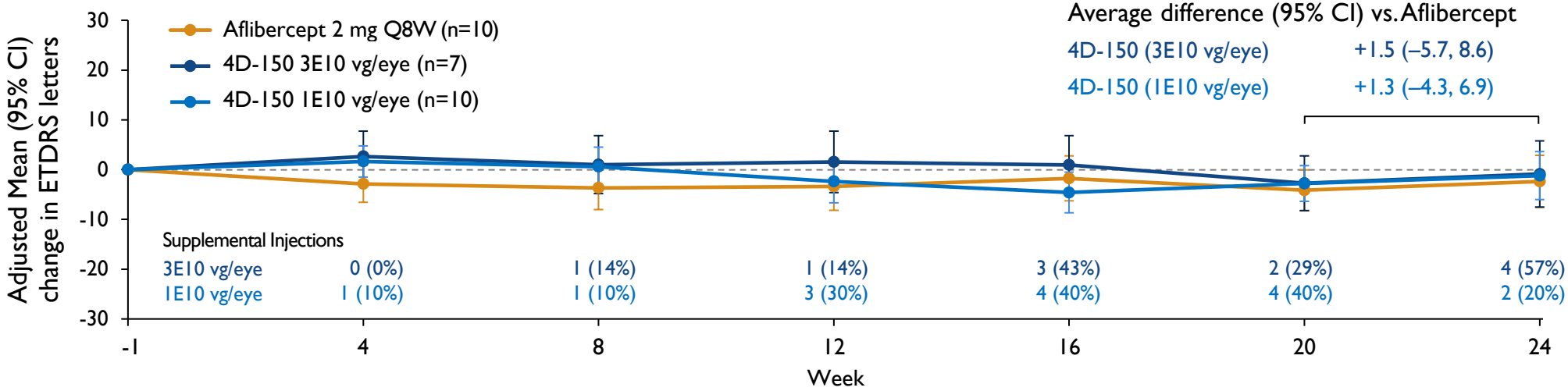
Best Corrected Visual Acuity By Supplemental Injection Status

Stable Visual Acuity Equivalent to Standard Aflibercept Through Week 24 in Both 4D-150 Dose Groups

Supplemental Injection-free
(4D-150, n=22)



Supplemental Injection (+)
(4D-150, n=17)

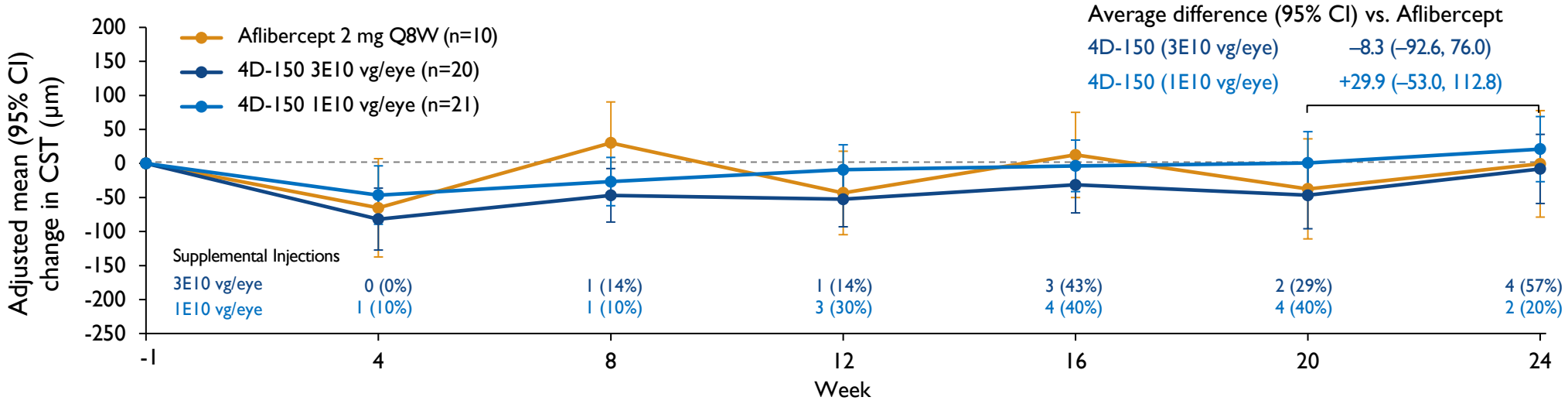


Baseline=Day -7. Adjusted mean (95% CI) estimated from a mixed–effect model for repeated measures (weeks 4-24) without imputation of missing values. Excludes participants (n=1 per dose group) with missing data due to early termination. ETDRS, Early Treatment Diabetic Retinopathy Study.

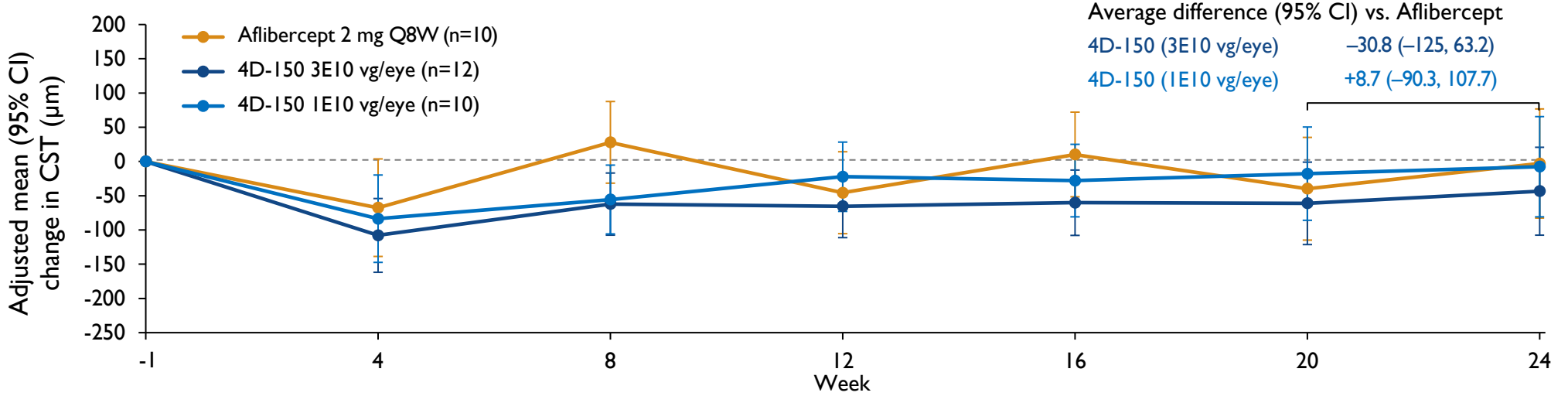
Central Subfield Thickness (CST): Supplemental Injection-free

4D-150 3E10 vg/eye: Sustained Reduction in CST and Reduced CST Fluctuation Compared to Aflibercept

Total Population
(4D-150, n=41)



Supplemental Injection-free
(4D-150 n=22)

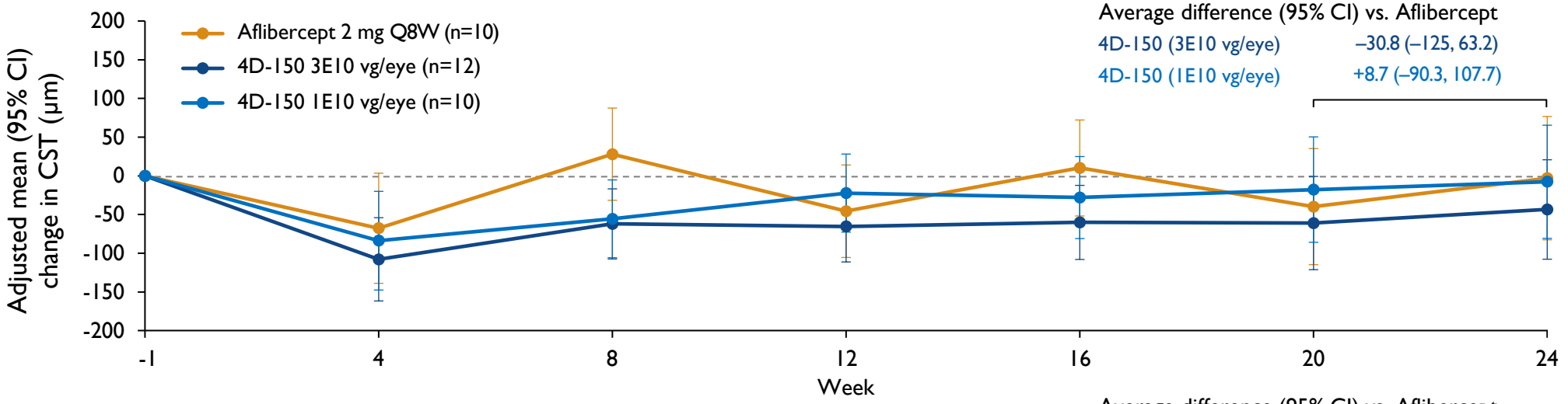


Baseline=Day -7. Adjusted mean (95% CI) estimated from a mixed–effect model for repeated measures (weeks 4-24) without imputation of missing values. Excludes participants (n=1 per dose group) with missing data due to early termination.

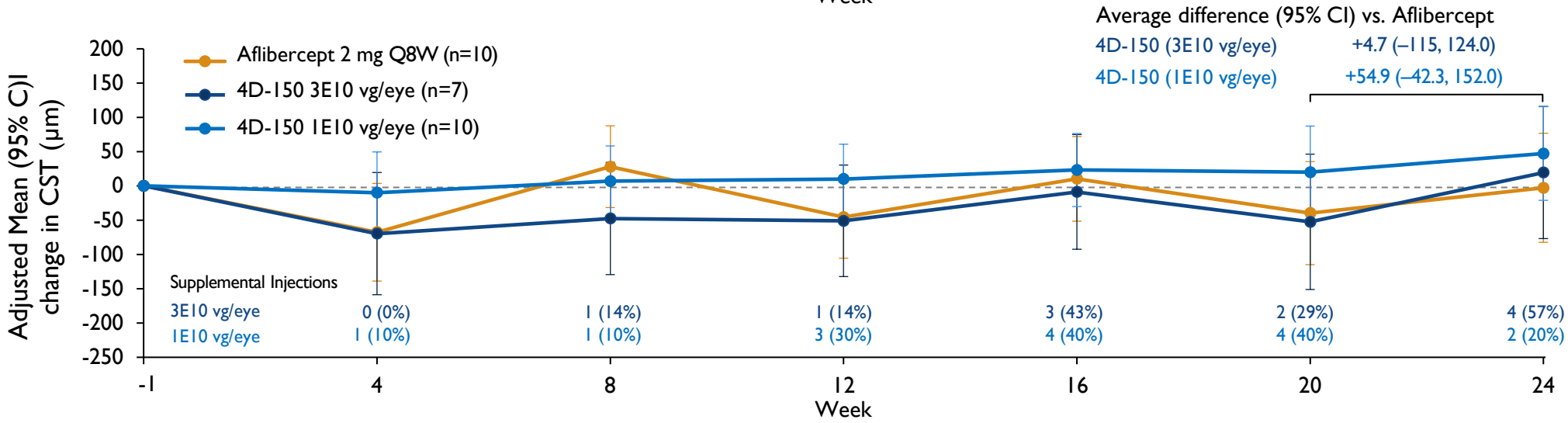
Central Subfield Thickness (CST): +/- Supplemental Injection

4D-150 3E10 vg/eye: Reduced CST Fluctuation Compared to Aflibercept

Supplemental Injection-free
(4D-150, n=22)



Supplemental Injection (+)
(4D-150, n=17)



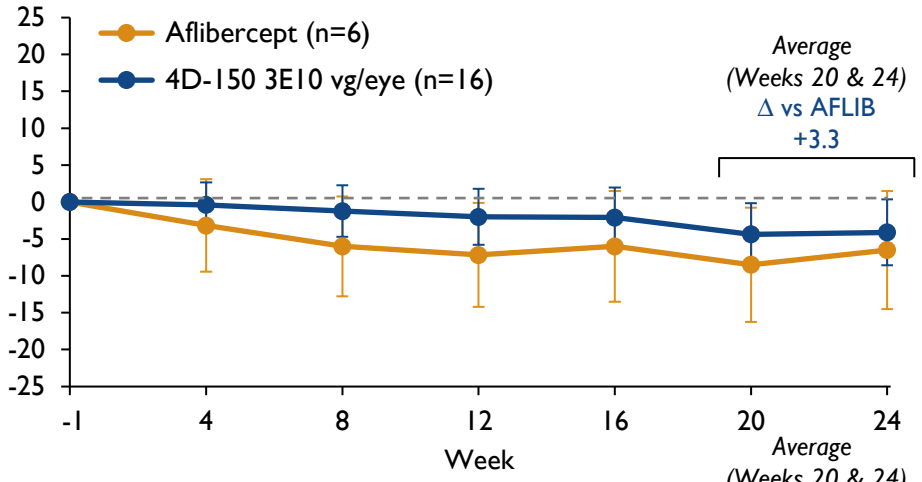
Baseline=Day -7. Adjusted mean (95% CI) estimated from a mixed–effect model for repeated measures (weeks 4-24) without imputation of missing values. Excludes participants (n=1 per dose group) with missing data due to early termination.

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

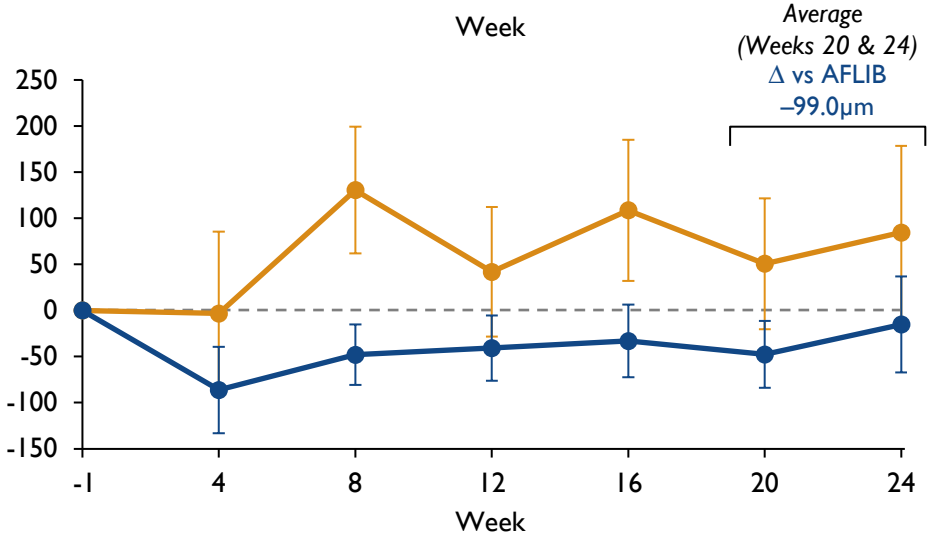
Preliminary Phase 3 Eligibility Criteria:

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

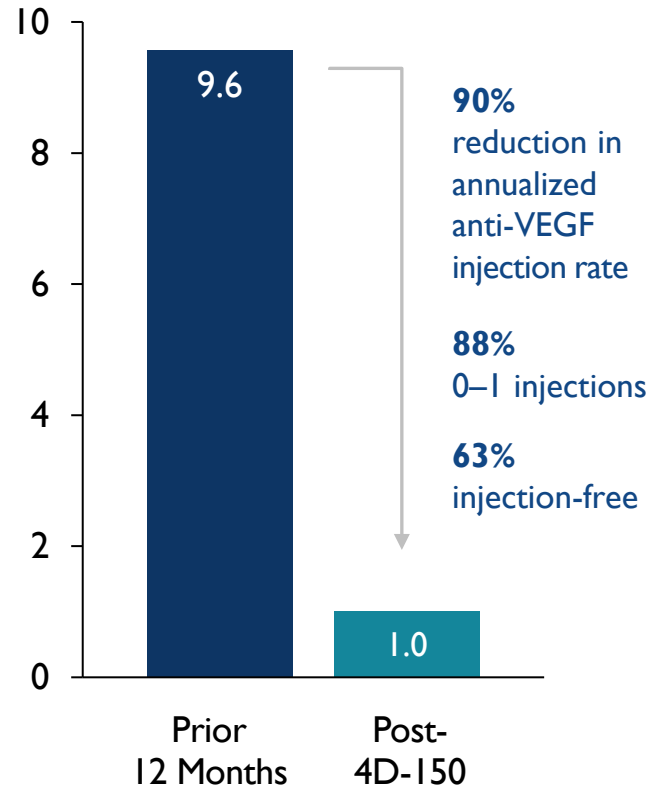
Adjusted mean ±95% CI change in BCVA (ETDRS letters)



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

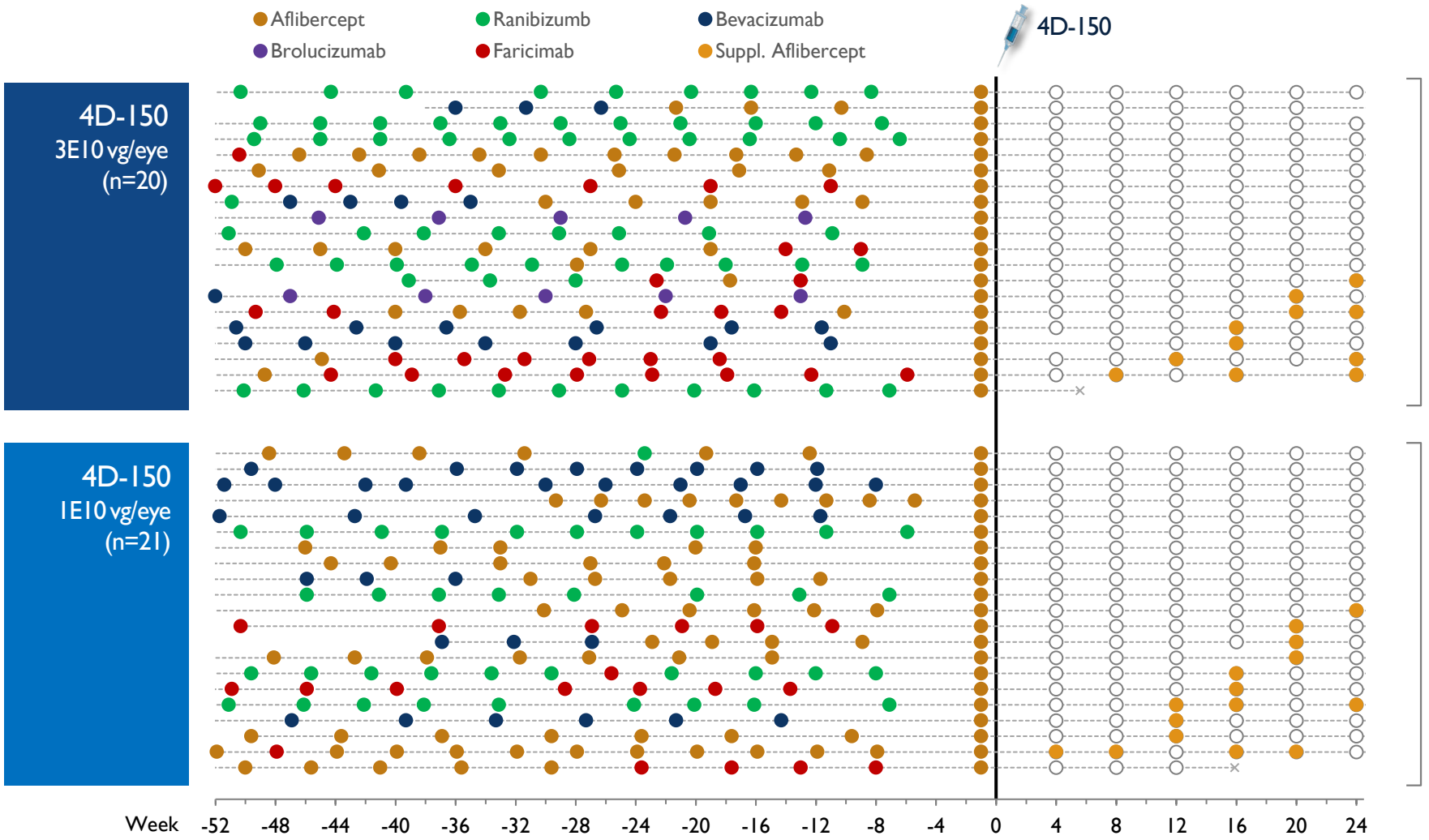


Anti-VEGF Injections



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

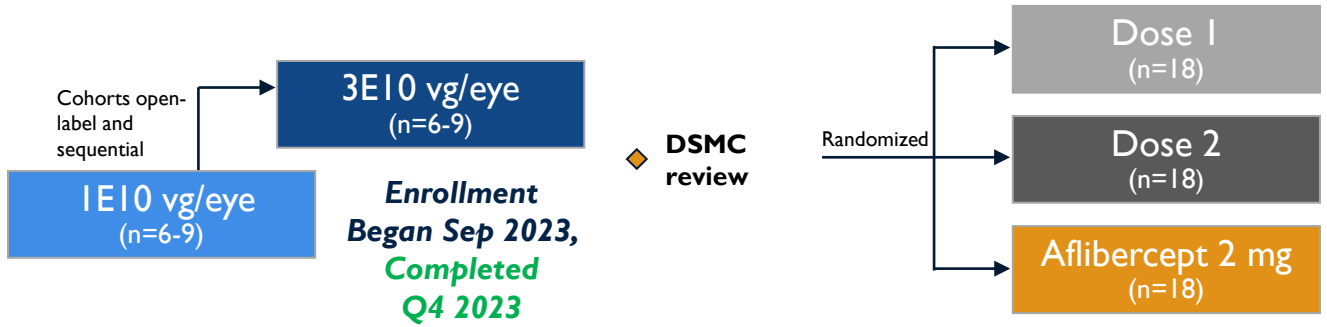
- **Phase 3 design based on initial feedback from FDA & EMA and clinical data to-date:**
  - Noninferiority (BCVA) 4D-150 **vs.** aflibercept 2mg Q8 week
  - **4D-150 3E10 vg/eye selected as study dose**
  - ~225 patients per arm
  - Broad wet AMD population, including patients with severe disease activity 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**

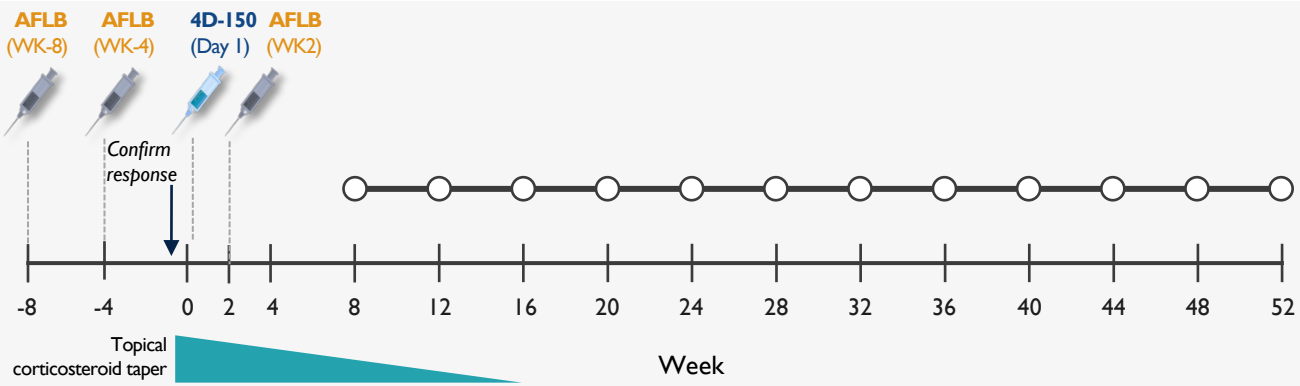
Phase 2 Study Evaluating 4D-150 in Diabetic Macular Edema, a 2nd Large Market Indication

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

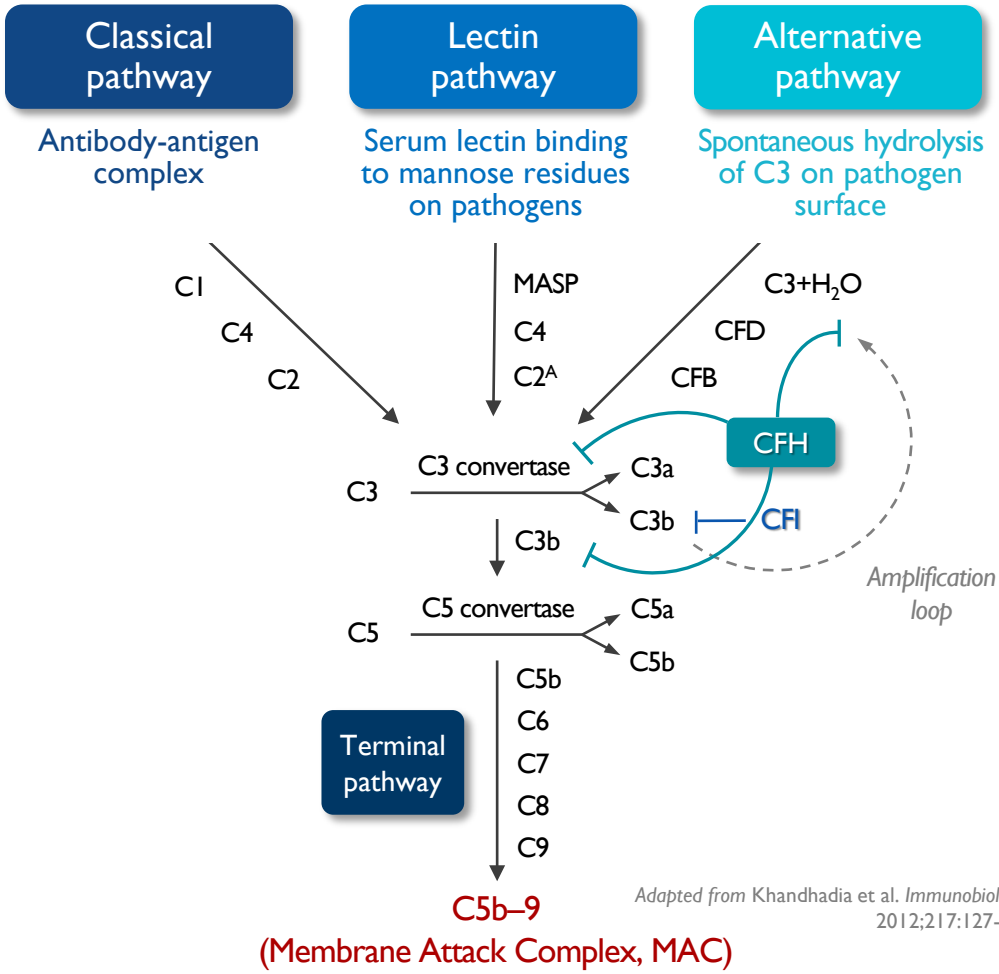
- Annualized number of aflibercept injections in the study eye

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

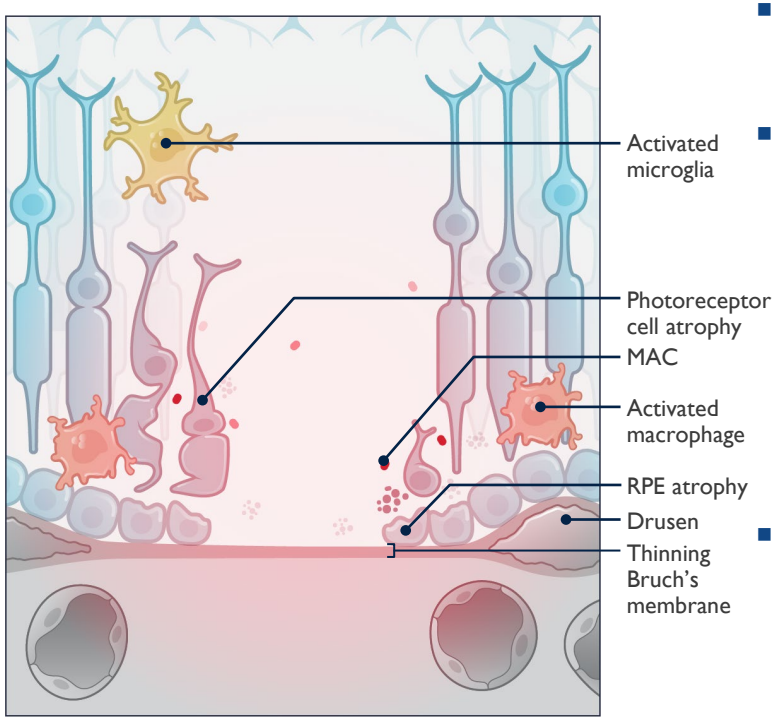
DME, Diabetic Macular Edema; BCVA, Best-Corrected visual acuity; CNV, choroidal neovascularization; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor

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.

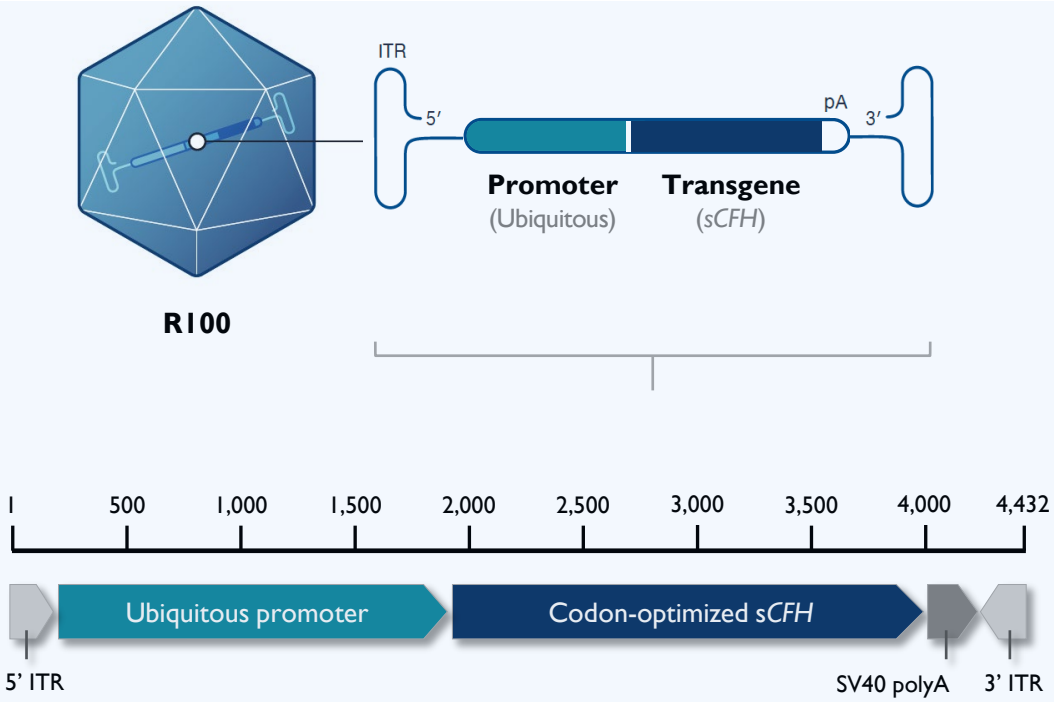
1. Rein, D. et al. *JAMA Ophthalmol.* 2022;140(12):1202-8 2. Manuelian et al. *J Clin Invest* 2003;111:1181–90. 3. Prosser et al. *J Exp Med* 2007;204:2277–83. 4. Syfovre [package insert]. Apellis Pharmaceuticals. 5. Izervay [package insert]. Iveric Bio, Inc.

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 begin enrolling in H2 2024**

4D-175: *sCFH*-Transgene Payload



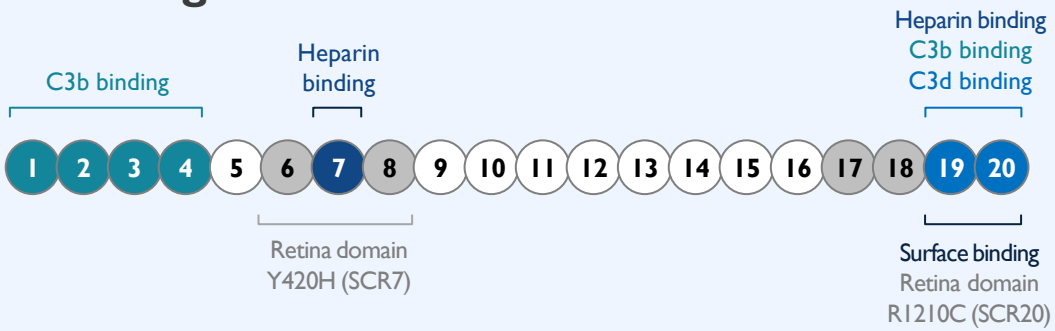
4D-175 Transgene Cassette

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]

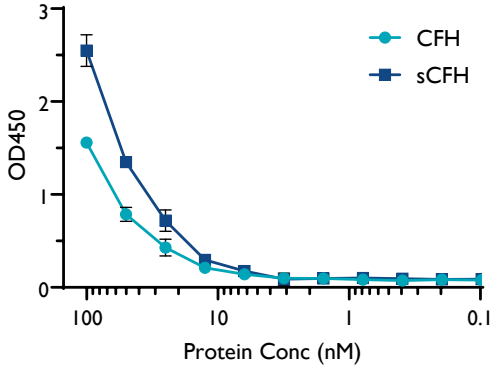


Short-form CFH (sCFH)

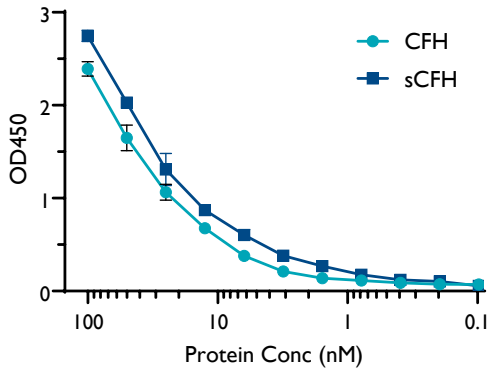
- Reduced size of the sCFH protein predicted to result in increased penetration of the RPE and choroid[2,3]

Pharmacological Activity

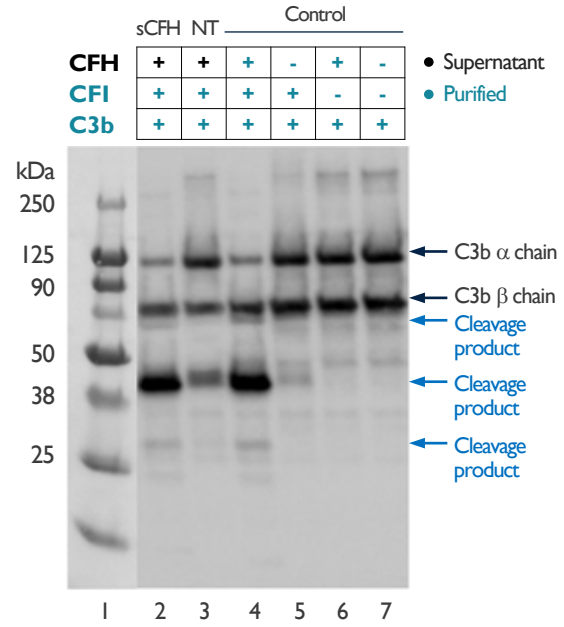
Heparin Binding



hC3b Binding



C3b Cleavage



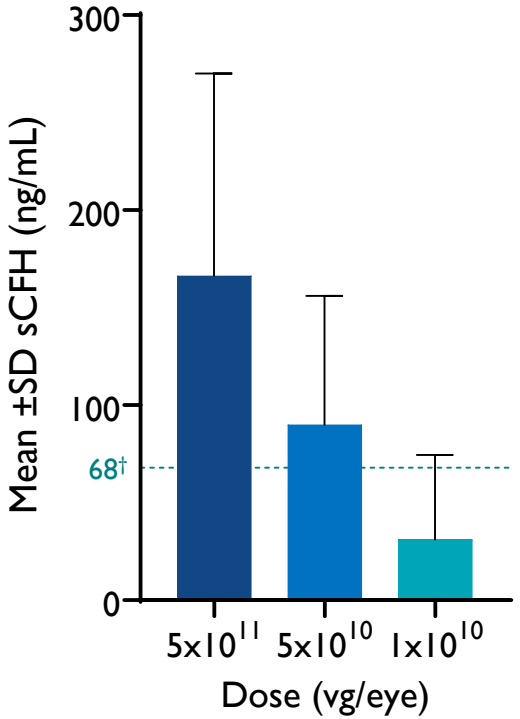
sCFH exhibits proper heparin and C3b binding and **inhibits complement activity *in vitro***

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.

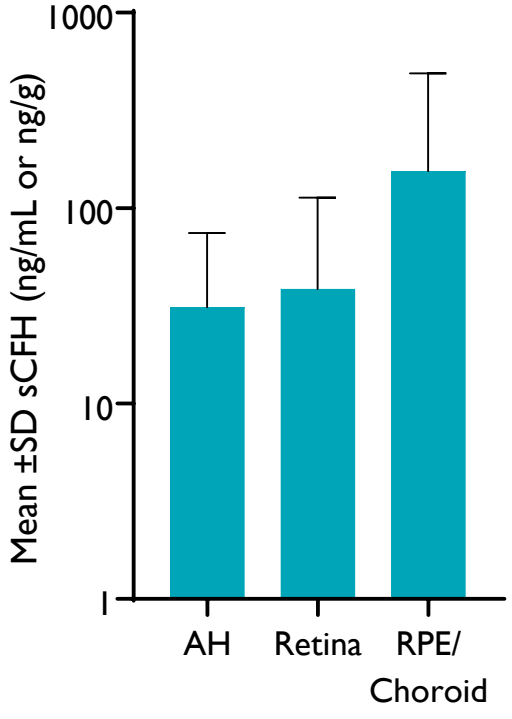
Target sCFH Concentration Levels Reached in Non-Human Primate Ocular Pharmacodynamics and Tolerability Study

4D-175 sCFH Ocular Biodistribution

Aqueous Humor*



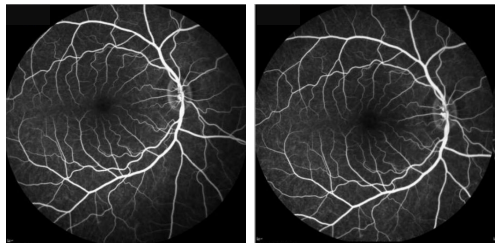
Ocular Distribution‡



4D-175 Safety and Tolerability

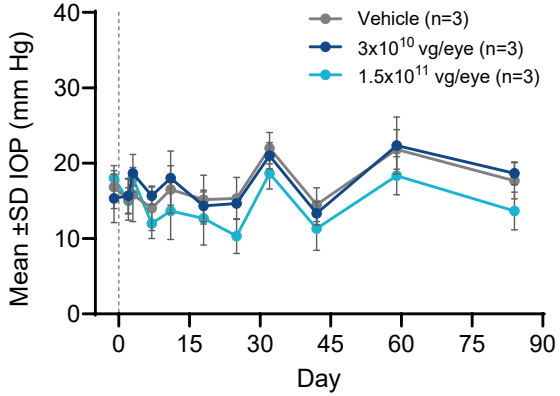
Fluorescein Angiography

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



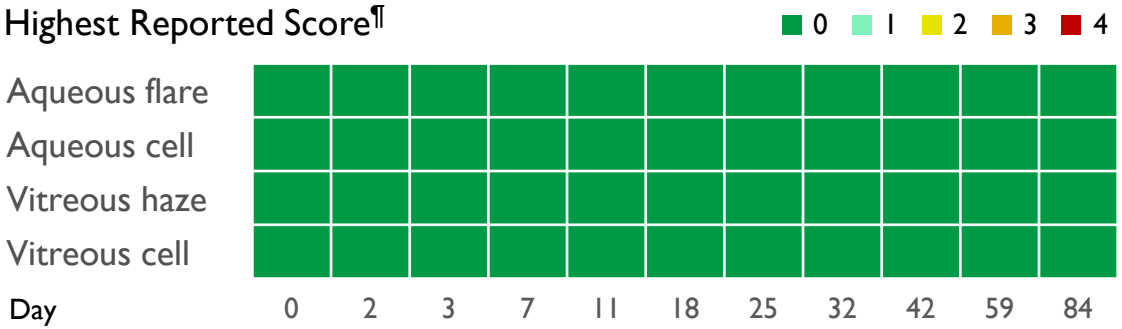
Baseline Week 12

Intraocular Pressure (IOP)



Ophthalmic Examination

Highest Reported Score¶



*Day 15 following IVT administration of 4D-175. †Target mean AH CFH concentration [1]. ‡1E10 vg/eye; tissue concentrations assessed at necropsy. ¶Uveitis score (3E10 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	PRISM	PRISM		▪ **July 17, 2024** Initial interim 24-week landmark analysis data from Phase 2 Population Extension (N=45) 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	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*	GAZE				▪ **H2:24** Begin enrollment of Phase 1 GAZE clinical trial

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

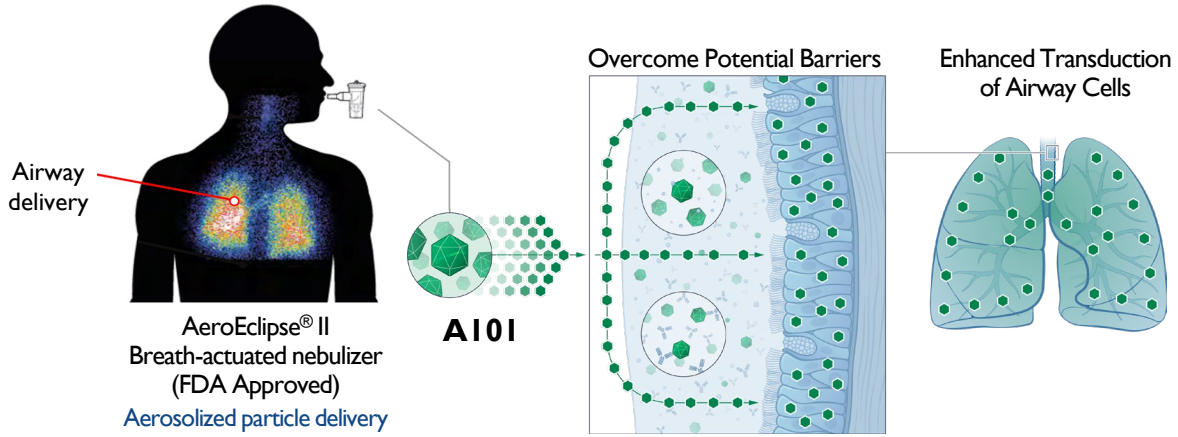
Prior aerosol gene therapy trials failed to achieve transgene expression in lung[1,2]; potential limitations:

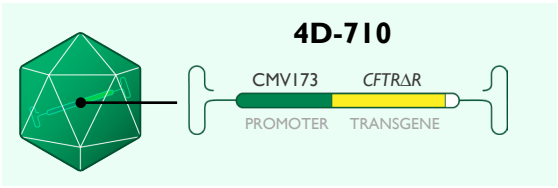
- ✕ Poor mucus penetration
- ✕ Inefficient airway cell transduction
- ✕ Suboptimal tissue tropism
- ✕ Susceptibility to clearance by human AAV immunity

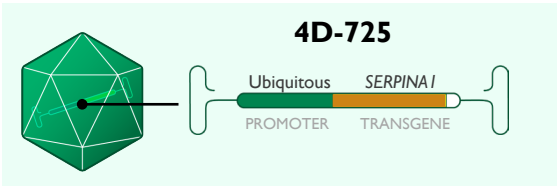
A101 invented at 4DMT to overcome these limitations:

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

Aerosolized A101-Based Genetic Medicines







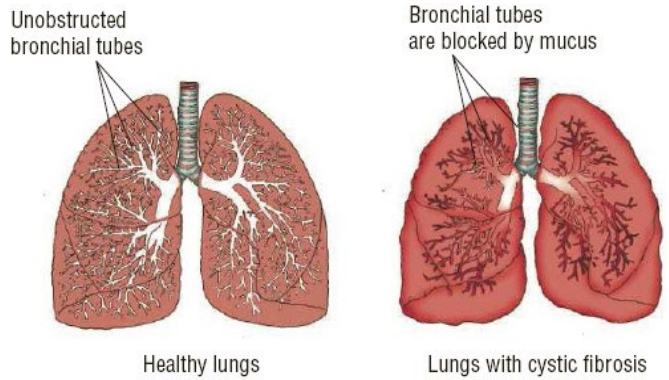
Product	Indication	Prevalence	Preclinical	Phase 1/2	Phase 3
4D-710	CF Lung Disease (mod. inelig/intol.)	*~15K WW*			
	CF Lung Disease (on modulators)	*~90K WW*			
4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EU*			

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

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
- **Lung function** ($ppFEV_1$) **annual decline:** –1 to –2.3%[1*,2]
- **Median survival (Pre-modulators):** ~40 years[3]



Epidemiology

- **~105,000[4,5] prevalence worldwide:**
  - ~40,000 prevalence in U.S. alone
  - ~1,000 incidence in U.S. alone

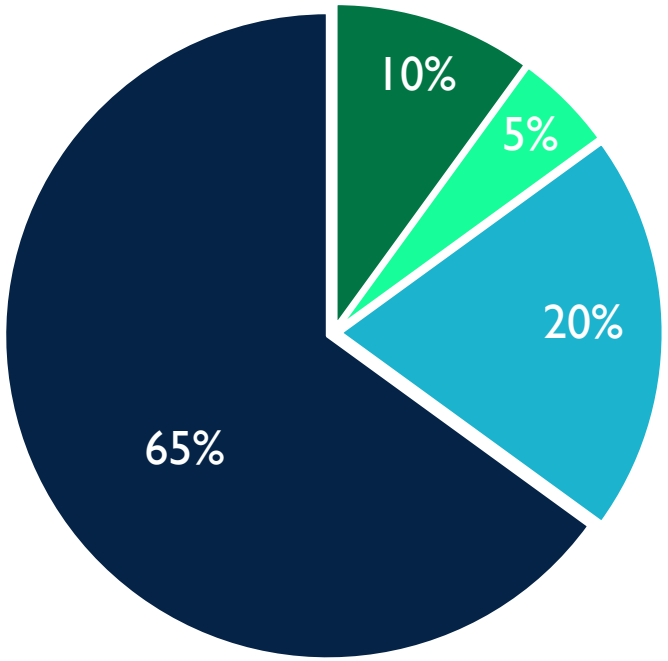
Standard of Care

- **Daily Supportive Care:**
  - Airway clearance (~100 mins)
  - Inhaled antibiotics & bronchodilators
- **Disease modifying CFTR modulators:**
  - **$9.9 billion** annually (2023)[6]

Illustration by Frank Forney. © 2016 Cengage Learning *Estimate based on *DF508* homozygous population, which appears to have a similar rate of decline as Class I (null) variant population. 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. Ramsey & Welsh. *Am J Respir Crit Care Med* 2017;195(9):1092–9. 4. Guo J et al. *Journal of Cystic Fibrosis* 2022; 21:456-62. 5. Cystic Fibrosis Foundation. 6. Vertex Pharmaceuticals FY 2023 financial results.
ppFEV1, percent predicted forced expiratory volume in 1 second.

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

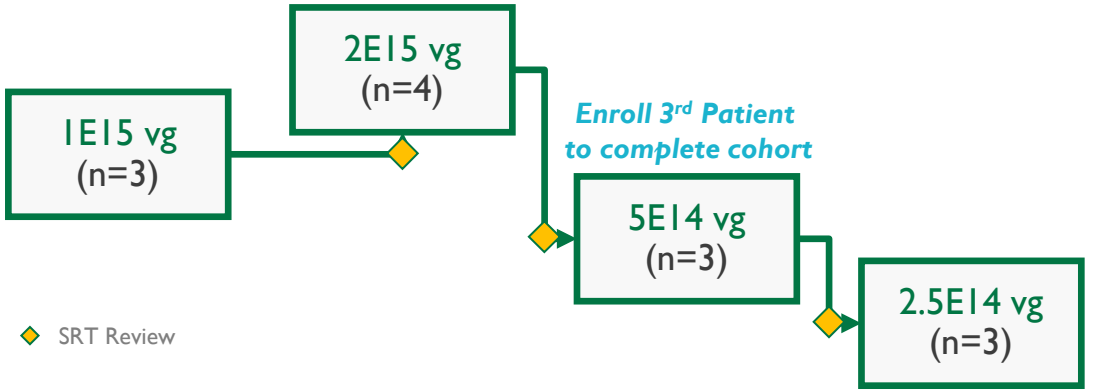
CFTR, cystic fibrosis transmembrane conductance regulator. 1. Based on assumptions derived from Middleton, 2019 and CFF registry analysis.

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

Generate Safety, Biomarker & Clinical Activity Data to Inform Selection of Phase 2 & 3 Dose

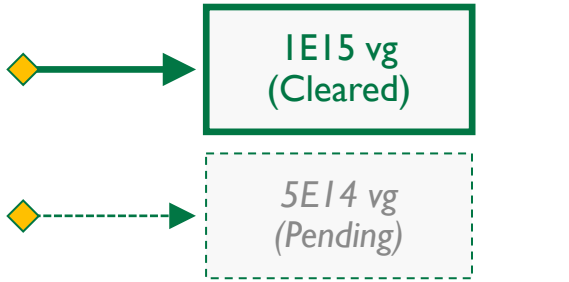
Phase 1 (Dose Exploration)

ppFEV$_1$ Eligibility Criteria: 50% to 100%



Phase 2 (Dose Expansion)

ppFEV$_1$ Eligibility Criteria: 50% to 90%



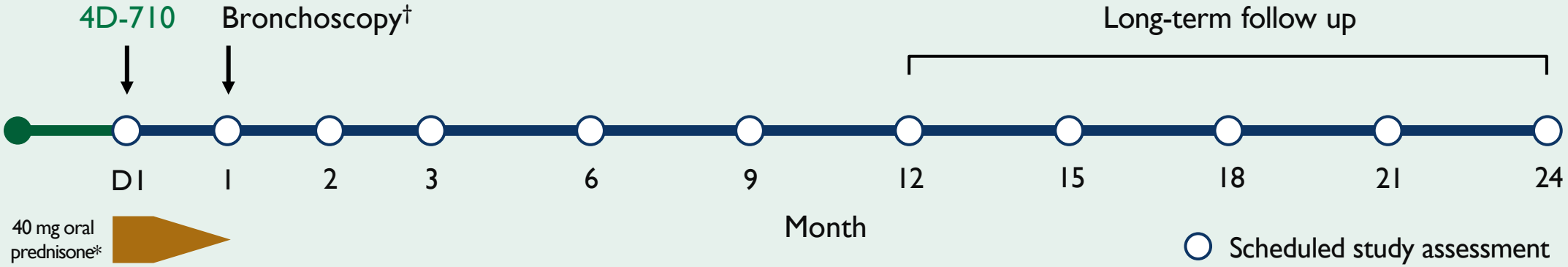
Expect to begin dosing (n= up to 9) H2 2024

Primary Objectives:

- **Phase 1:** Dose ranging to characterize safety & biomarkers
- **Phase 2:** Expand in selected dose to confirm clinical activity for Phase 3

Key Endpoints:

- Safety & tolerability
- Lung biomarkers
- Clinical activity



*28-day taper. †Endobronchial biopsy (4D-710 transgene and protein expression), pending protocol amendment to allow for 2nd biopsy beyond 12 months. ppFEV1, percent predicted forced expiratory volume in 1 second; SRT, Safety Review Team.

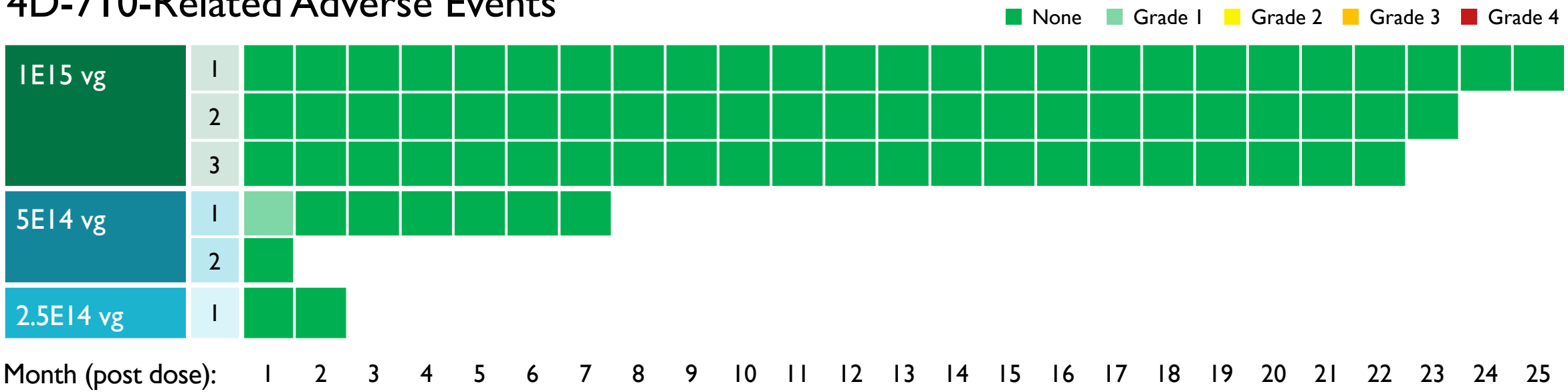
AEROW To-Date Enrolled pwCF Ineligible or Intolerant to Modulators with a Broad Range of Disease Activity, 5 with Pre-Existing Immunity to A101

	2E15 vg				1E15 vg			5E14 vg		2.5E14 vg
Participant #	1	2	3	4	1	2	3	1	2	1
Age, y	37	27	32	69	36	24	20	42	39	25
Sex	Female	Male	Female	Female	Male	Male	Female	Female	Female	Male
Race/Ethnicity	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic White	Non-Hispanic Black	Non-Hispanic White
CFTR modulator status	Ineligible	Ineligible	Ineligible	Intolerant	Intolerant	Ineligible	Ineligible	Intolerant	Ineligible	Ineligible
Historical Sweat chloride, mmol/L†	84	96	103	114	74	103	110	107	134	120
$ppFEV_1$	90	56	80	86	83	69	95	100	77	58
CFQ-R-R score	78	72	89	78	72	61	83	72	78	28
Anti-A101 Ab	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Positive	*Pending*	Negative
A101-specific T cells	Positive	Negative	Negative	Negative	Negative	Positive	Positive	*Pending*	*Pending*	*Pending*

Best available data as of May 24, 2024. †Sweat chloride normal range ≤29 mmol/L, Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation (2017). pwCF = people with cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R-R, Cystic Fibrosis Questionnaire–revised respiratory domain; NAb, neutralizing antibodies.

Aerosolized 4D-710 (Up to 1E15 vg) Was Well Tolerated

4D-710-Related Adverse Events

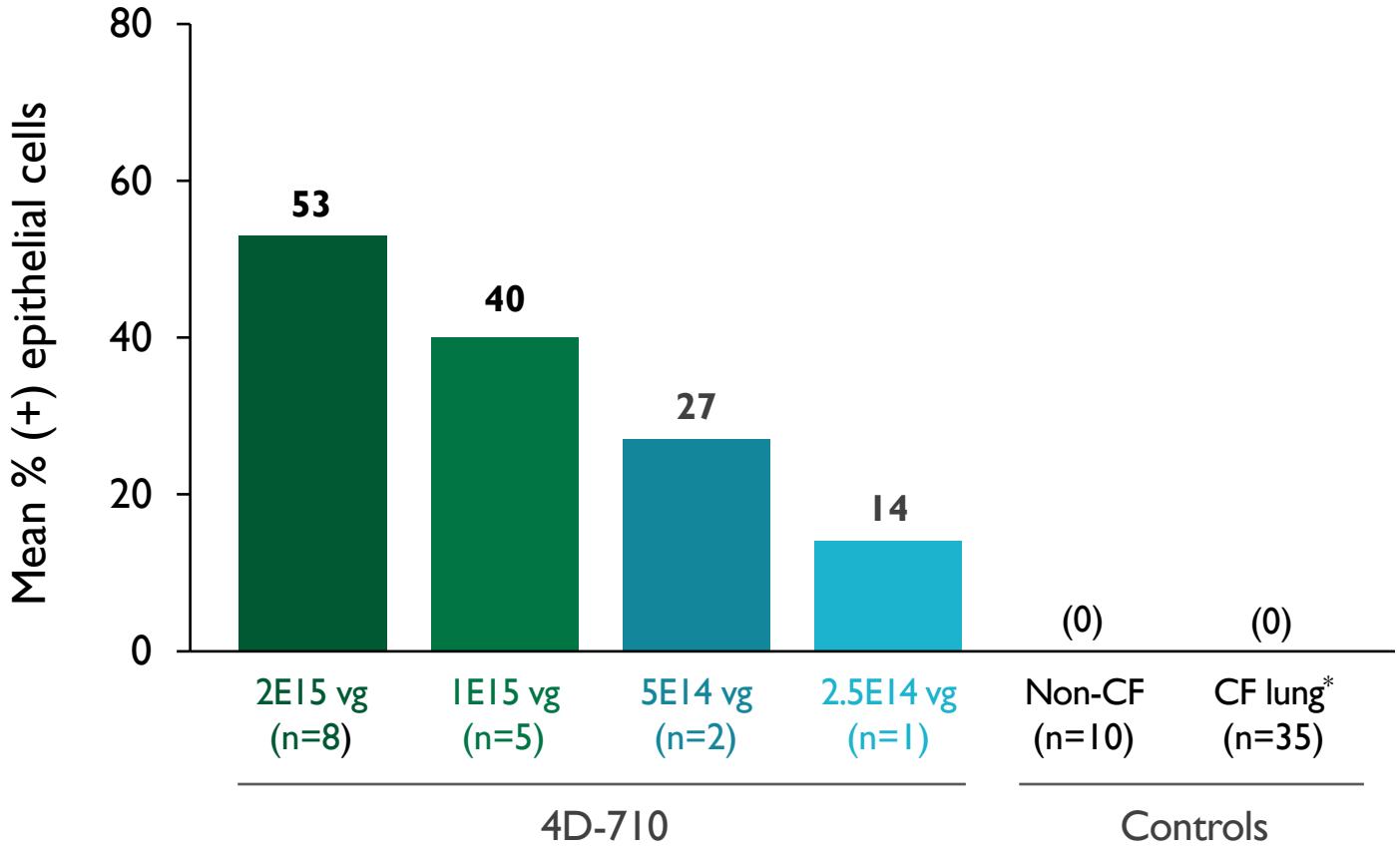


- Administration of aerosolized 4D-710 well tolerated
  - No dose-limiting toxicities
  - No 4D-710–related SAEs
  - No clinically significant 4D-710-related adverse events after administration
- No inflammation or toxicity in lung biopsies samples

Best available data as of May 24, 2024.

Dose-dependent *CFTRΔR* RNA Expression Following 4D-710 Administration

CFTRΔR RNA (ISH): mean % (+) airway epithelial cells

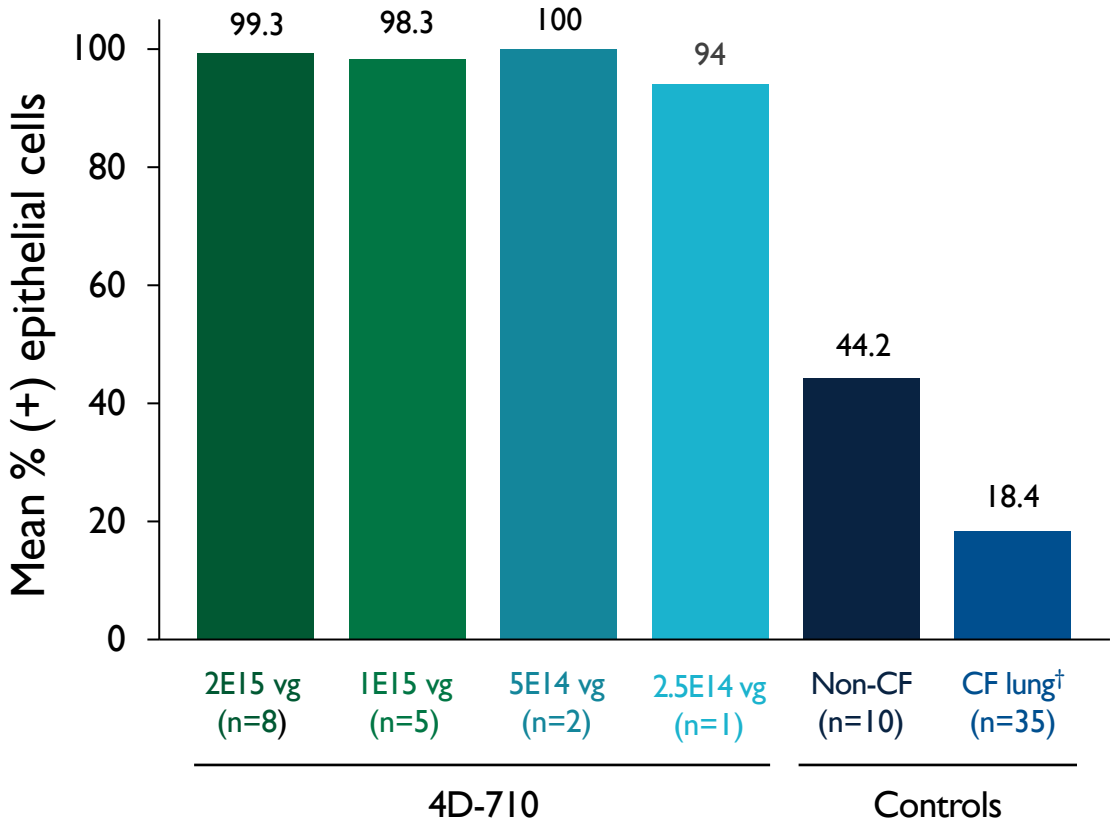


- Dose-dependent *CFTRΔR* mRNA expression in bronchial epithelial cells
- No *CFTRΔR* mRNA expression observed in commercial non-CF and CF lung samples
- Commercial non-CF samples positive for endogenous *CFTR* mRNA expression

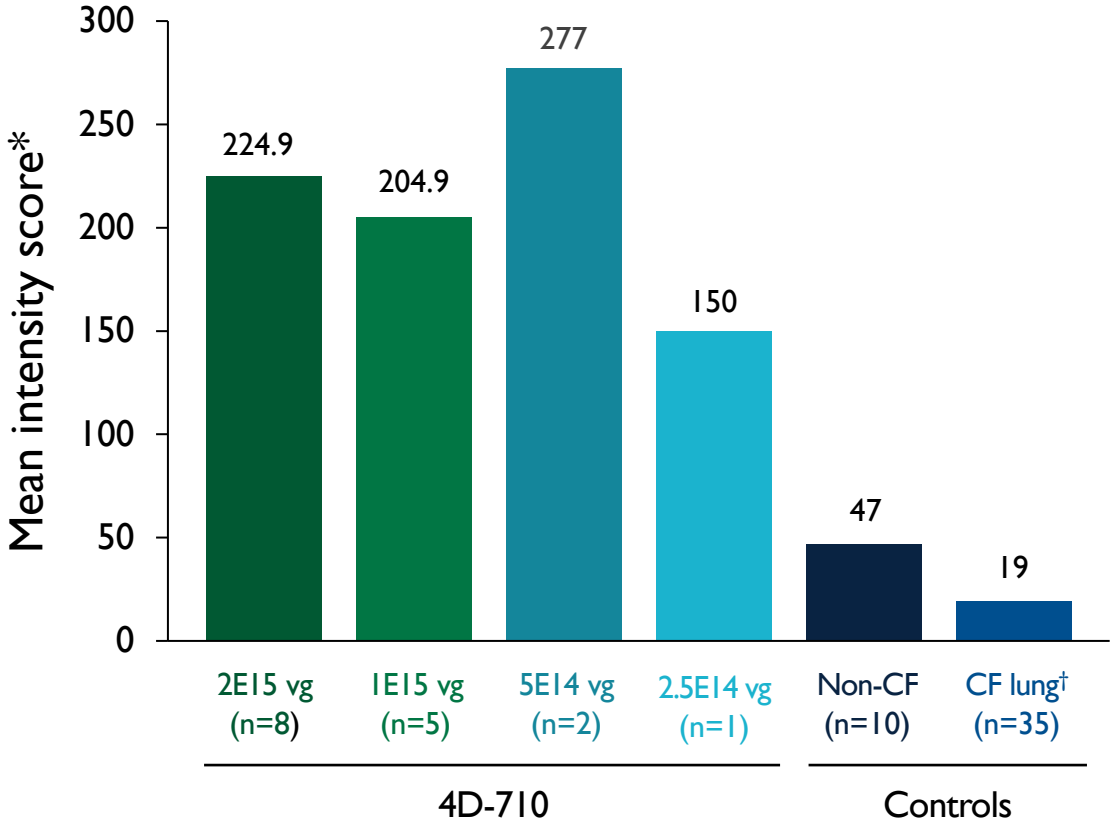
Best available data as of May 24, 2024. Quantification by Visiopharm® AI Machine Learning Analysis. Number shown below each group indicates the number of lung samples. *Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were ΔF508 homozygous mutations. CFTR, cystic fibrosis transmembrane conductance regulator; ISH, in situ hybridization.

Widespread 4D-710–Mediated CFTR Protein Expression at All Doses and in All Participants

CFTR (+) Epithelial Cells (IHC)



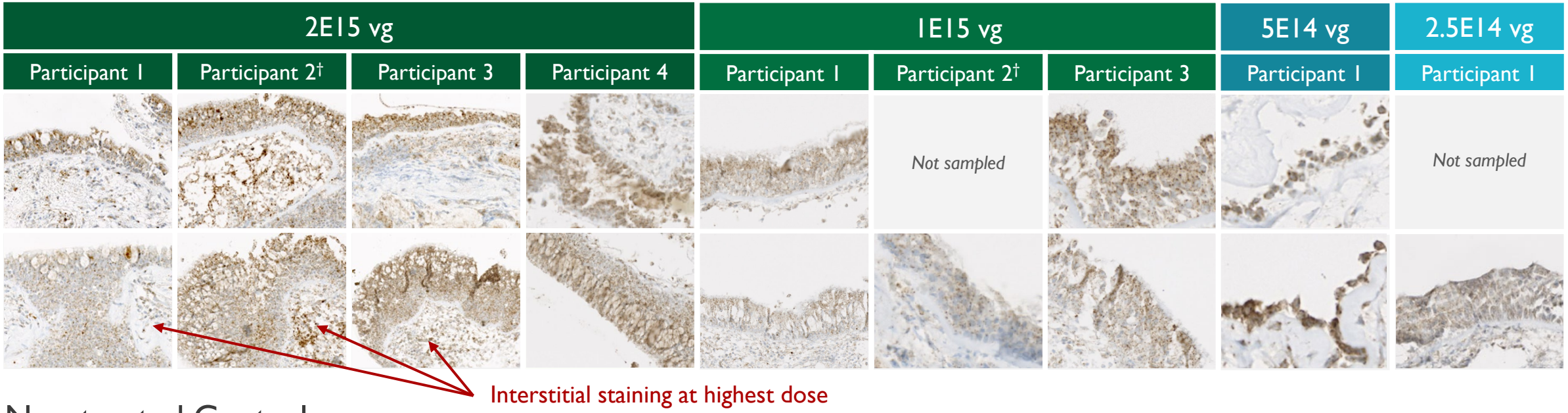
CFTR Staining Intensity (IHC)*



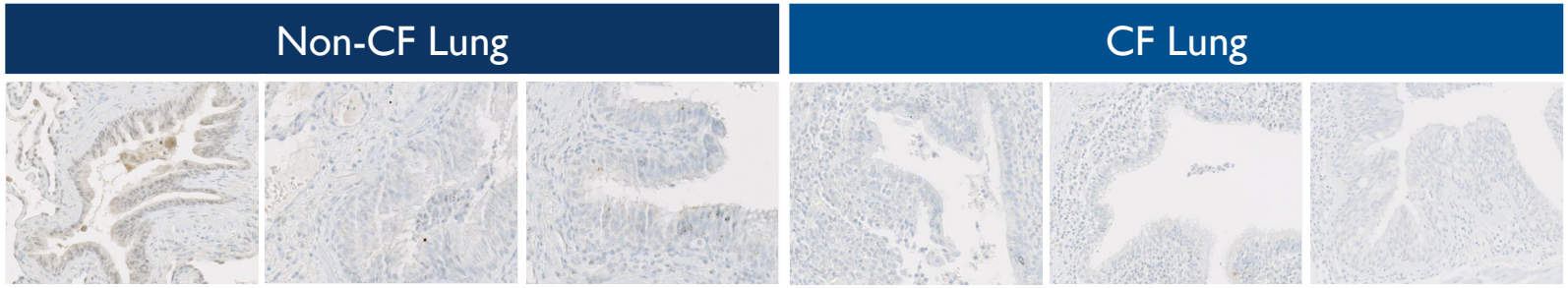
Best available data as of May 24, 2024. Quantification by Visiopharm AI Machine Learning Analysis. Number shown below each group indicates the number of lung samples. *H-score. †Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were ΔF508 homozygous mutations. IHC, immunohistochemistry.

Widespread & Consistent CFTR Protein Expression: 100% of Samples

4D-710 Treated



Non-treated Controls

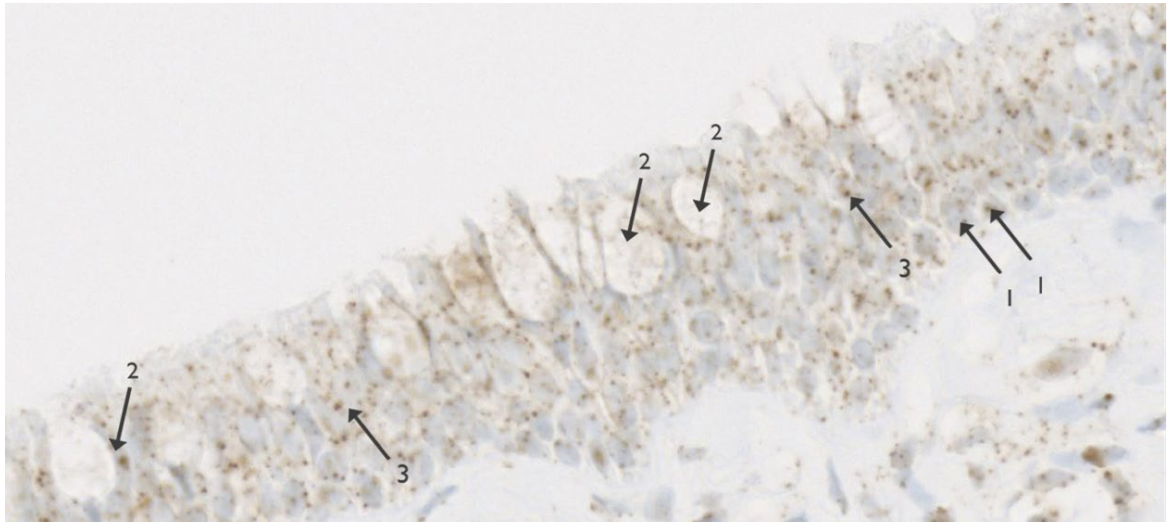


Best available data as of May 24, 2024. *Representative images, endobronchial biopsy samples obtained from the left secondary carina (row 1) and right middle lobe (row 2). †Endobronchial biopsy performed at Week 8.

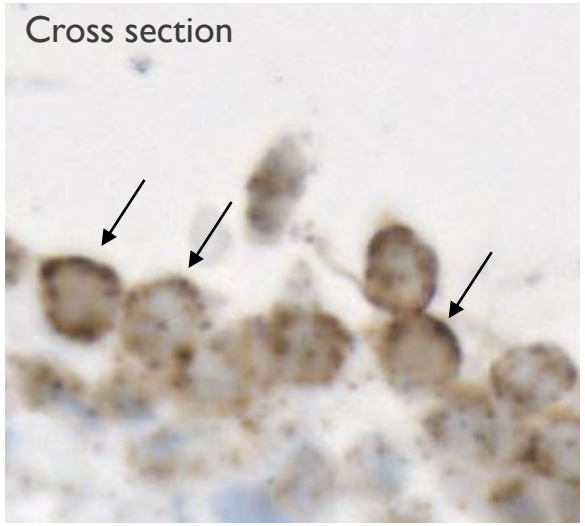
CFTR Protein Expression Observed in Multiple Airway Cell Types

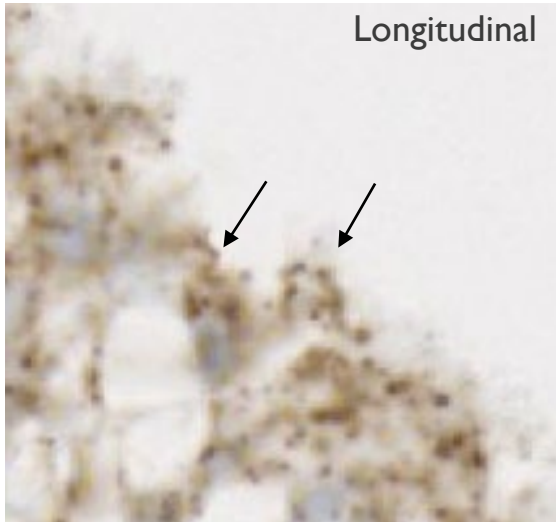
CFTR Protein Expression (IHC) Following Administration of 4D-710: Secretory, Ciliated & Basal Cells

CFTR Protein Expressed in Multiple Cell Types*



Localization to Apical Region†





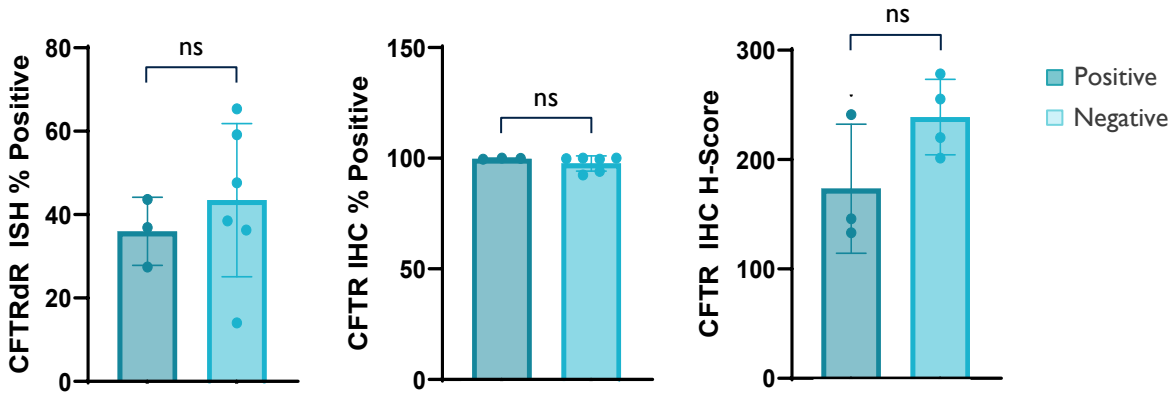
(**1**) Basal cells (**2**) Goblet cells (**3**) Columnar ciliated cells

Best available data as of May 24, 2024. *Image from 1E15 vg participant. †Images from 2E15 vg participants. CFTR, cystic fibrosis transmembrane conductance regulator. IHC, immunohistochemistry.

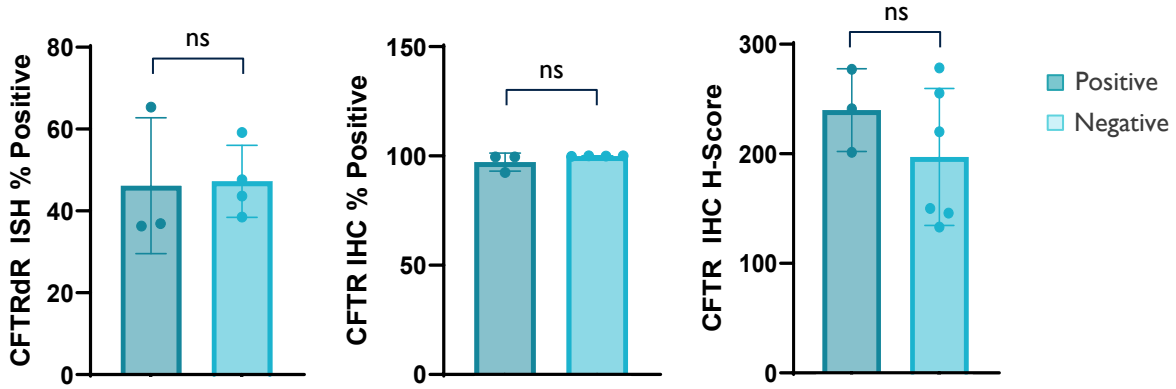
Pre-existing A101 Immunity and Transgene-mediated Protein Expression

Pre-existing A101 Immunity Did **NOT** Affect *CFTRΔR* RNA or CFTR Protein Expression

CFTR Expression According to Baseline Anti-A101 Antibodies



CFTR Expression According to Baseline A101-specific T Cells



Pre-existing Anti-A101 Capsid Antibodies

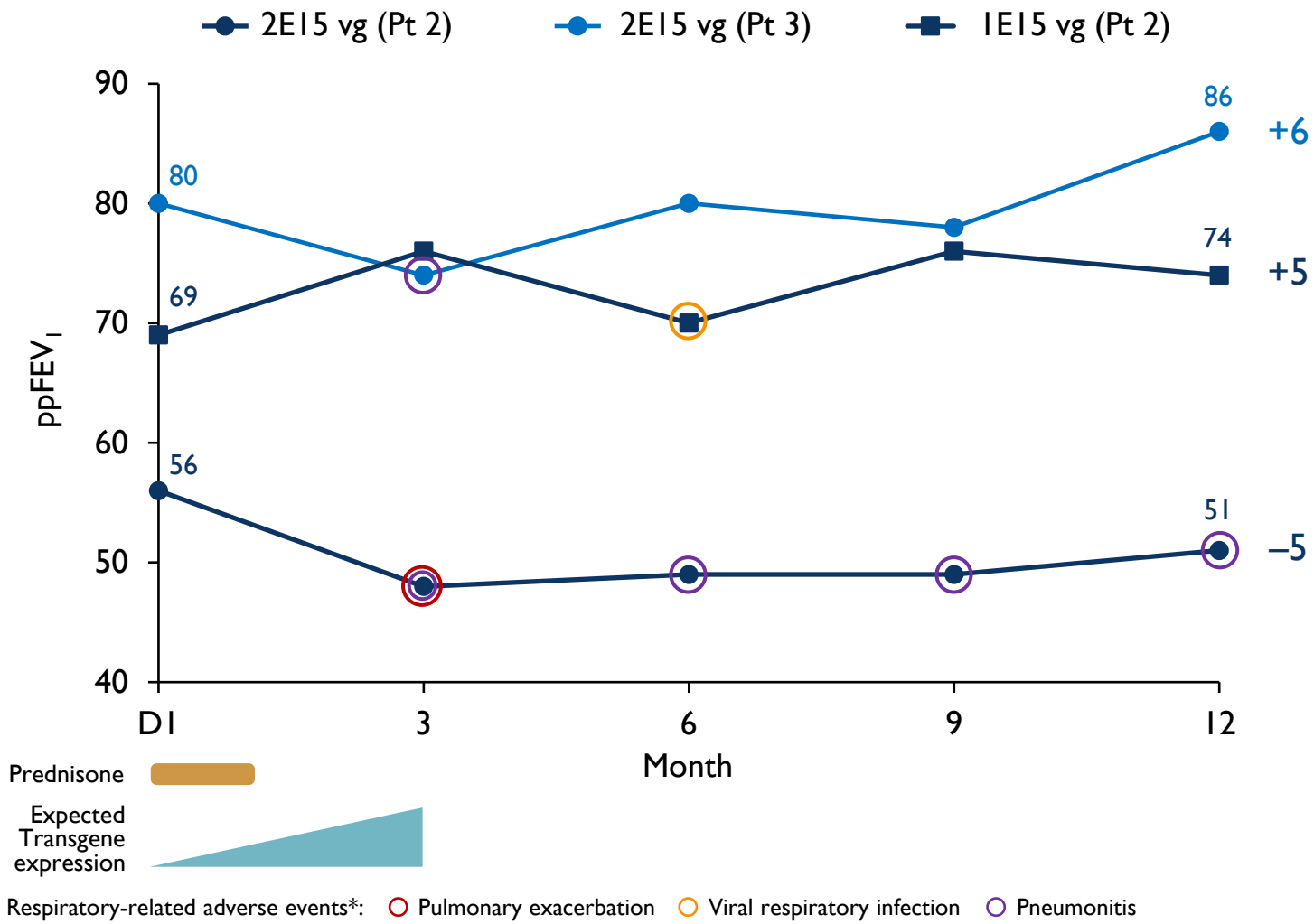
- 3/9 positive for pre-existing A101 capsid antibodies*
- **No significant difference in mRNA/protein expression** between participants with (n=3) and without (n=6) pre-existing A101 antibodies
- No observed effect of pre-existing antibodies on safety

Pre-existing A101-specific T cells

- 3/7 positive for pre-existing A101-specific T cells†
- **No significant difference in mRNA/protein expression** between participants with (n=3) and without (n=4) pre-existing A101-specific T cells

Best available data as of May 24, 2024. *Results pending for n=1 participant (5E14 vg group). †Results pending for n=2 and n=1 in the 5E14 vg and 2.5E14 vg cohorts, respectively.

Two of Three Participants with Mild to Moderate ppFEV$_1$ Impairment at Baseline Showed Improvement at 12 Months

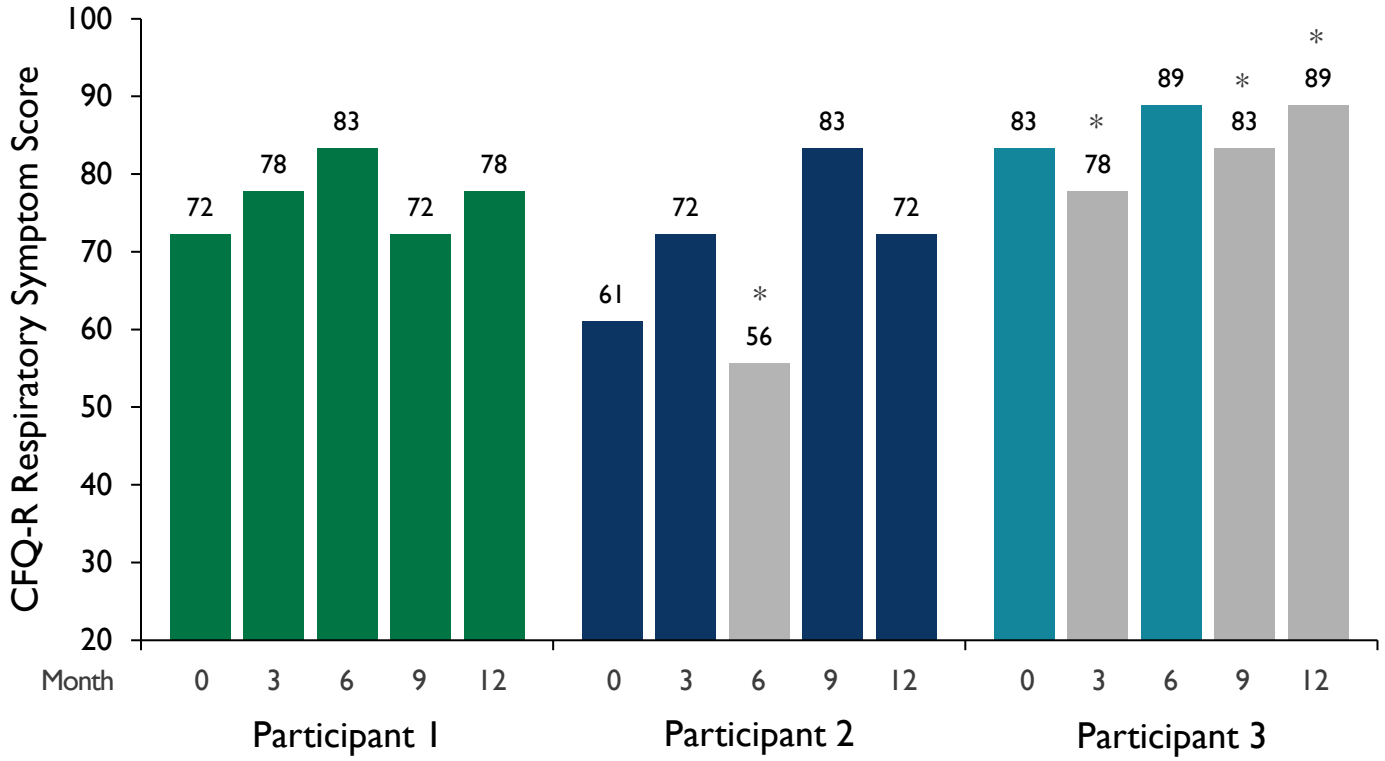


- Three participants had a baseline ppFEV$_1$ ≤80% and >6 months of follow up
- Two showed improvement in ppFEV$_1$ at 12 months
  - 2E15 vg (n=1): +6%
  - 1E15 vg (n=1): +5%

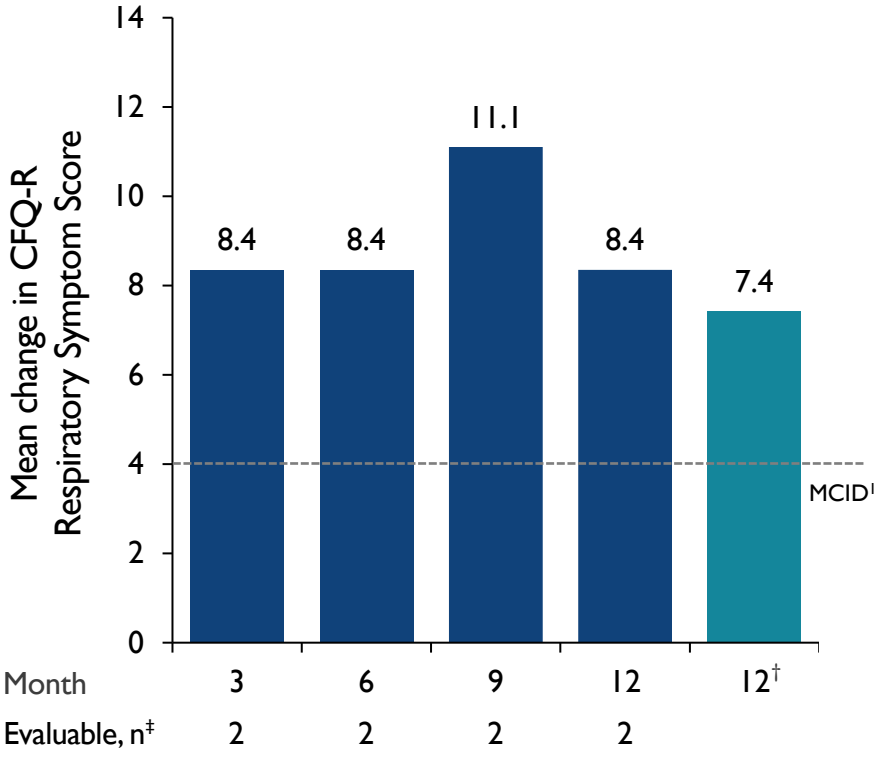
Best available data as of May 24, 2024.

4D-710 (1E15 vg): Durable Improvement in CFQ-R-R Score

CFQ-R Respiratory Symptom Score



Mean Change in CFQ-R-R Score



Best available data as of May 24, 2024. *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.

Totality of Clinical & Biomarker Data To-date Supports **1E15 vg** as Intended Phase 2 Expansion Dose, 5E14 vg Dose Pending Additional Follow-Up

Dose Selection Criteria:		Target Profile	2E15 vg (n=4)	1E15 vg (n=3)	5E14 vg (n=1)	2.5E14 vg (n=1)
Expression	*CFTRΔR* RNA expression (ISH)	**≥15% cells**[1,2]	✓	✓	✓	✗
	CFTR protein expression (IHC)	**≥15% cells**[1,2]	✓	✓	✓	✓
	Cell types transduced	**Basal cells & secretory cells**	✓	✓	✓	✓
		No/limited expression in interstitial cells	✗	✓	✓	✓
	Pre-existing A101 Immunity	**No effect on expression**	✓	✓	✓	*Pending*
Safety & Tolerability	Safety & tolerability	**No ≥Grade 3 related AEs, No related SAEs**	✗	✓	✓	✓
Clinical Activity	$ppFEV_1$ (at 6-12 months)	**>4.5% change from baseline**	✓	✓	*Pending*	*Pending*
	CFQ-R-R (at 6-12 months)	**>4 points change from baseline**	*Not interpretable*	✓	*Pending*	*Pending*
				Cleared	*Pending*	

Best available data as of May 24, 2024.
*Both events reported by one study participant (Participant 2) 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.

Robust Safety, Biomarker, and Clinical Activity Profile Generated To-date Supports Advancement into Phase 2 Dose Expansion

- Expect to **begin enrollment in Phase 2 Expansion stage in H2 2024** starting with 1E15 vg (anticipate enrolling n= up to 9)
  - In parallel, complete evaluation of 5E14 vg as a potential 2nd Phase 2 dose by completing enrollment & follow-up of a 3rd participant in the 5E14 vg cohort in Phase 1 Dose Exploration
  - 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
    3. Open cohort for 4D-710 in pwCF on CFTR modulators with persistent moderate to severe lung disease; expect to begin enrollment **in H2 2024**
  - Anticipate sharing interim data from AEROW in **mid-2025** after completing enrollment and f/u of Phase 2
- 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; ppFEV1, percent predicted forced expiratory volume in 1 second

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-R), frequency of pulmonary exacerbations

Accelerated Approval

Additional FDA/EMA discussions to follow additional AEROW clinical and lung biomarker data in pwCF with lower 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-R: 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 **AAV** **AAV101** **Aerosol** 	4D-710	Cystic Fibrosis Lung Disease (modulator ineligible / intolerant)	*~15K WW*			AEROW		▪ **Mid-2025** Interim data update from Phase 1/2 AEROW clinical trial ▪ **H2 2025** Pivotal trial initiation
		Cystic Fibrosis Lung Disease (on-modulators)	*~90K WW*			AEROW		▪ **H2 2024** Initiation of enrollment of on-modulator cohort
	4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EUMM*					▪ **H2 2024** Program update

4DMT

CARDIOLOGY 

Vector: C102

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

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

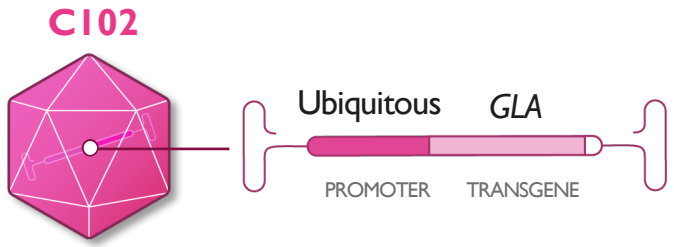
Cardiac disease is the most common cause of death (75%)[1] in Fabry disease

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

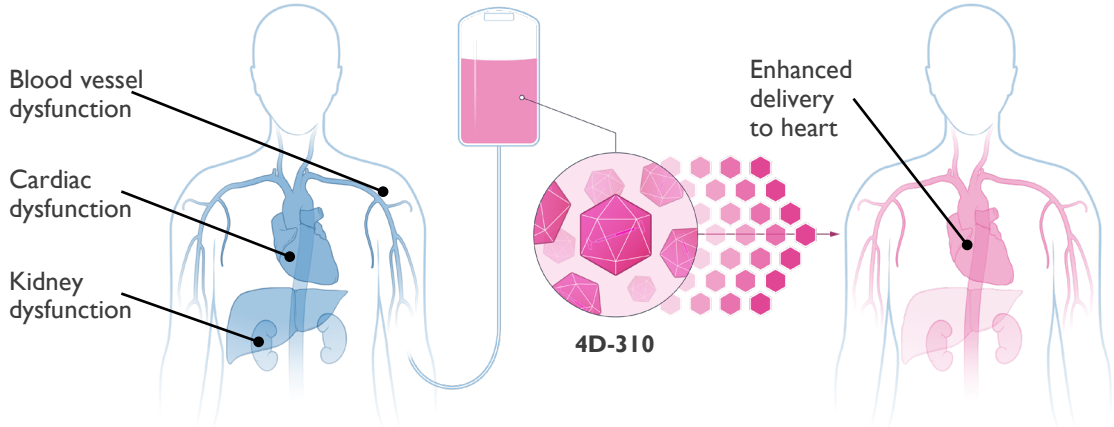
4D-310



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

Transgene: *GLA* (encodes AGA enzyme)

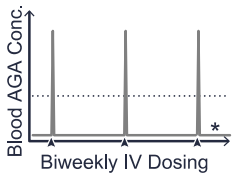
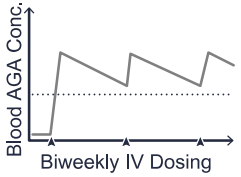
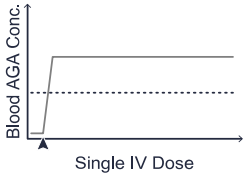
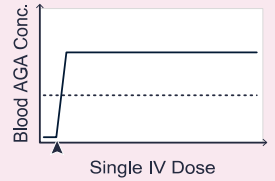
Promoter: Ubiquitous



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.

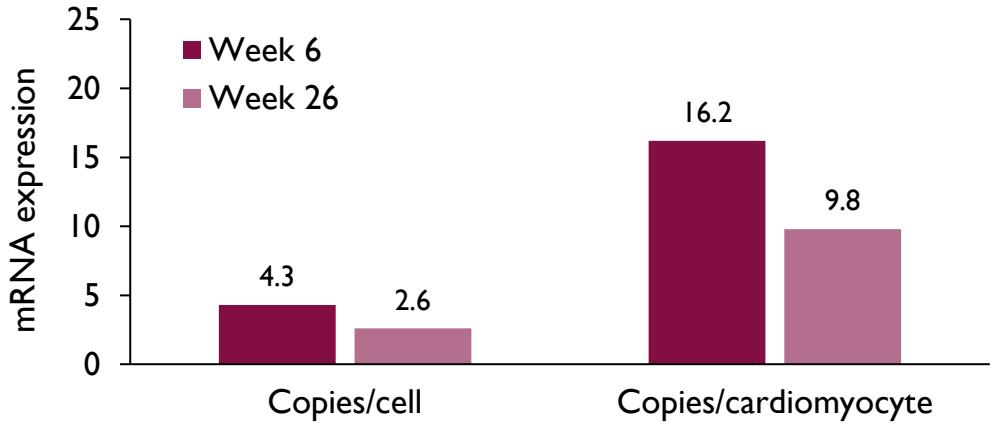
Baseline Patient Characteristics

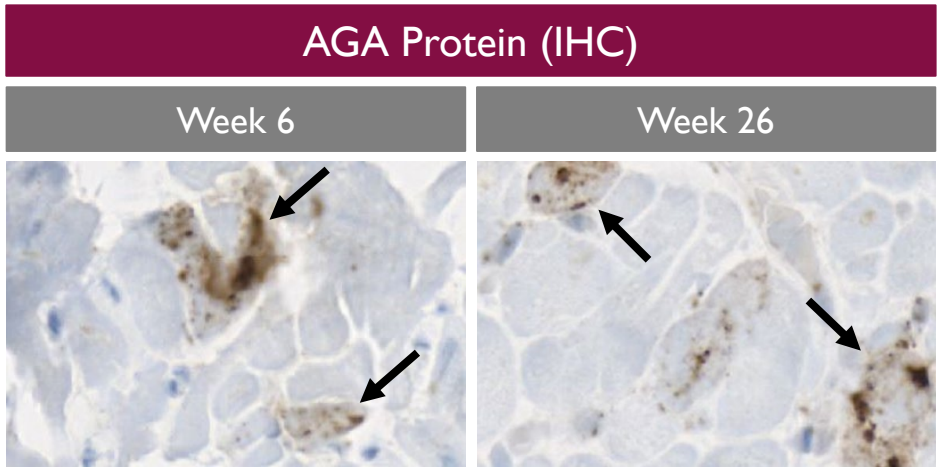
	INGLAXA 1				INGLAXA 2	
Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Disease classification	Classic	Classic	Classic	Late onset	Late onset	Late onset
GLA variant	c.1023A>C	c.708G>T	c.974G>A	c.671A>G	IVS4+919 G>A	c.644 A>G
Serum AGA activity, nmol/hr/mL*	0.42	0.00	0.30	0.06	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

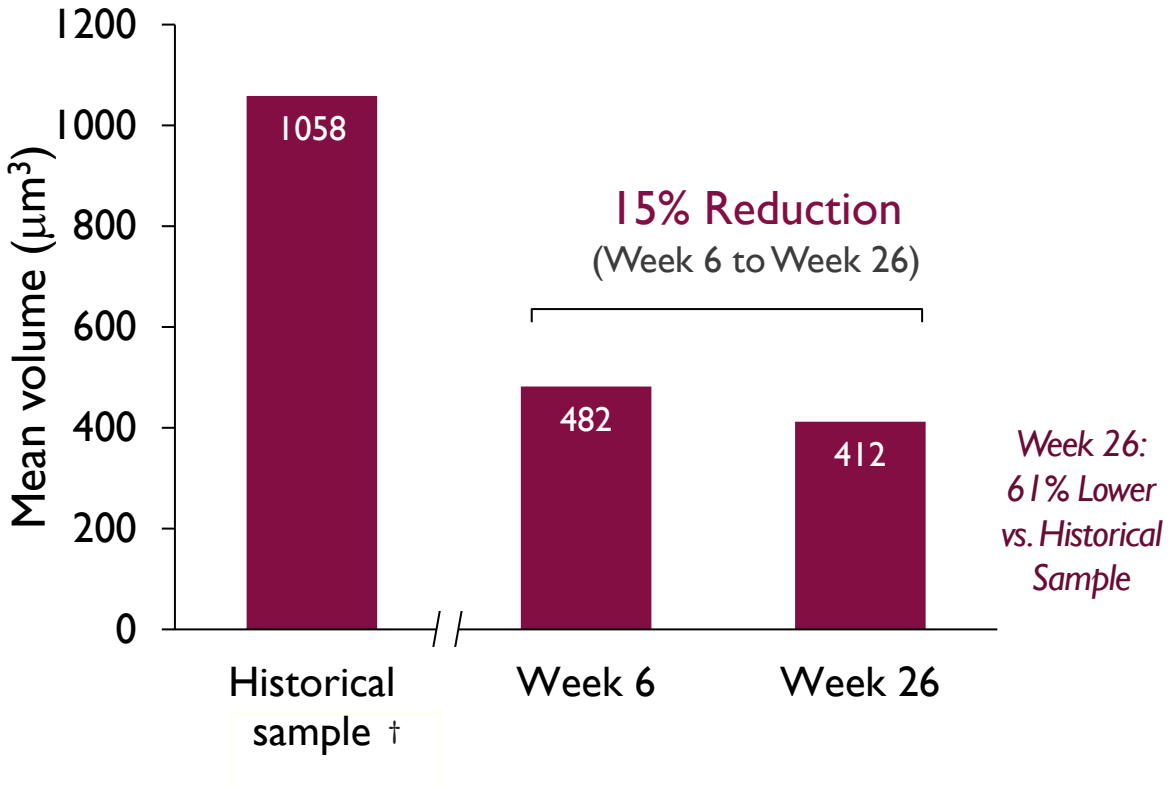




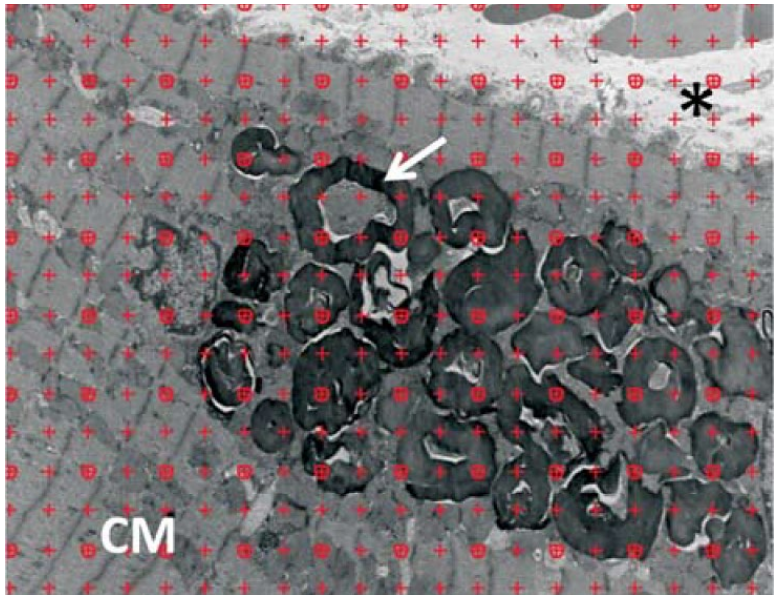
*Male (57 y) with late-onset Fabry disease. †Calculated based on an estimated 30% ratio of cardiomyocytes to total heart cells. IHC, immunohistochemistry; ISH, *in situ* hybridization; qPCR, quantitative polymerase chain reaction; RT-qPCR, reverse transcription-qPCR.

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**

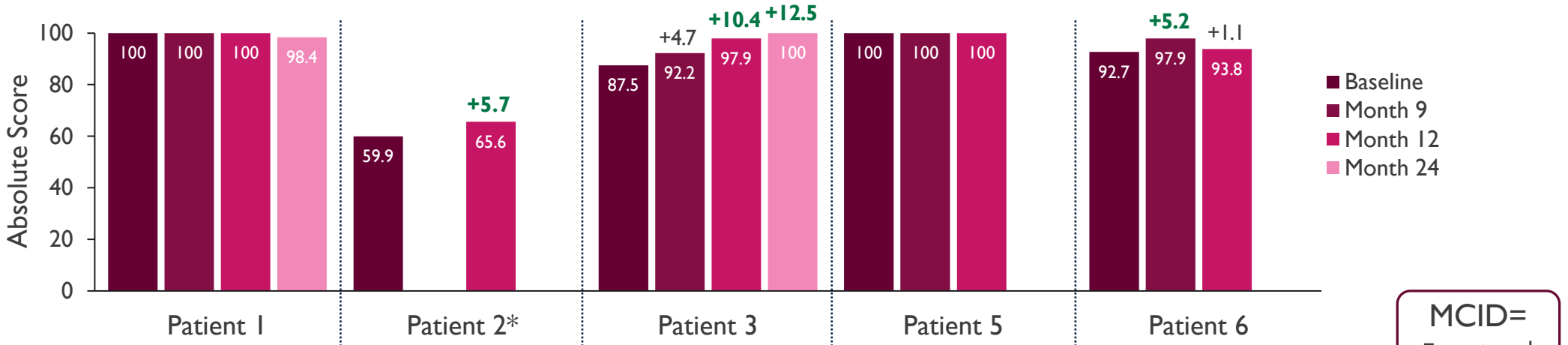
MCID=
1.5 mL/kg/min[1]

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.

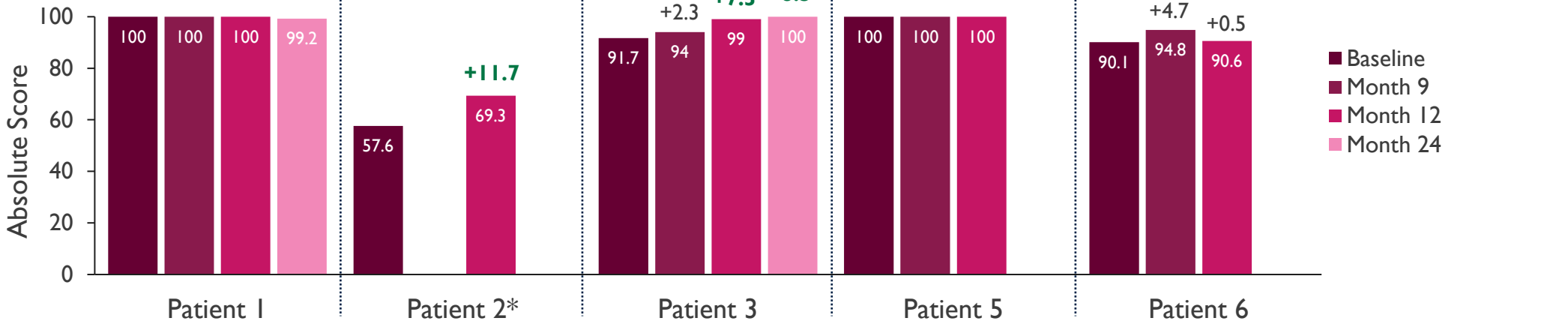
Kansas City Cardiomyopathy Questionnaire (KCCQ): Improved or Stable QoL in All Evaluable Participants

Clinical Summary Score



MCID= 5 points[1]

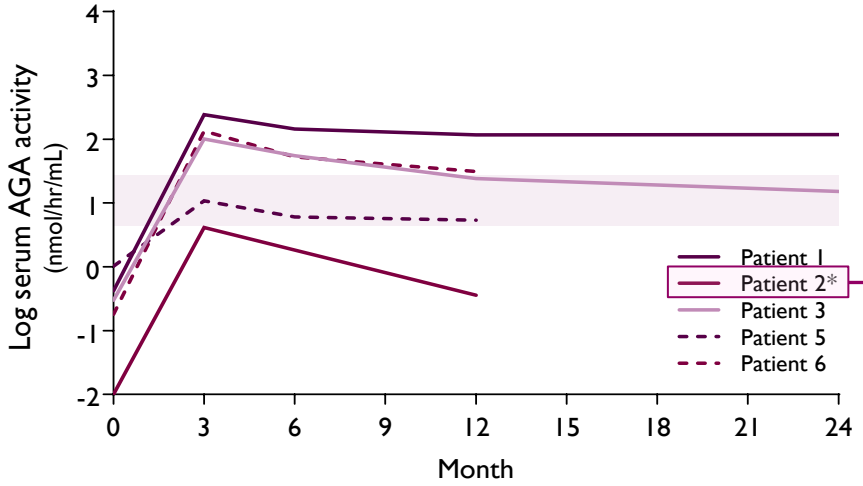
Overall Summary Score



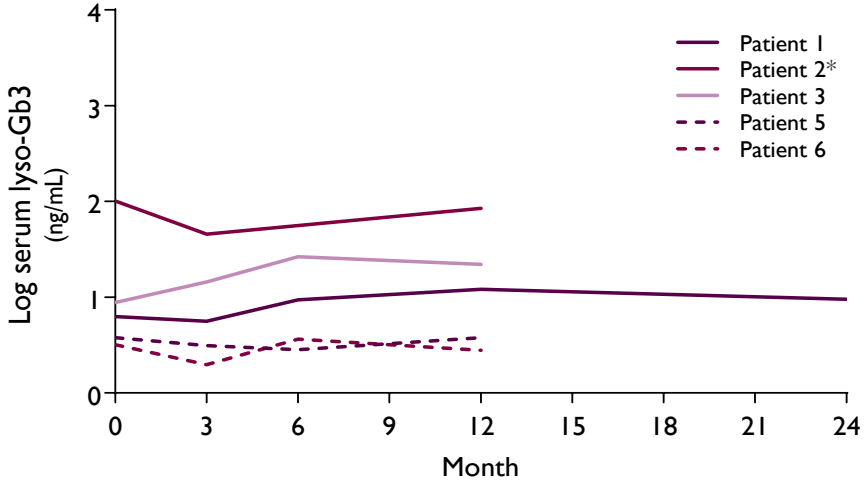
Scores range from 0 to 100 (higher score=less severe); minimal clinically important difference (overall summary score), 5 points [1]. *High antibody titer; entered study off ERT. 1. Spertus JA et al. JACC 2020;76:2379–90.

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 evaluating IV 4D-310 combined with rituximab & sirolimus is complete and **submitted to FDA**

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=45) at ASRS: **July 17, 2024**
		Update on Phase 3 clinical trial design: **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**	Begin enrollment of Phase 1 GAZE clinical trial: **H2 2024**
Pulmonology	4D-710 for **CF**	Interim data update from Phase 1/2 AEROW clinical trial: **Mid-2025** 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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