4DMT

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

Corporate Presentation | November 2024

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

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4DMT

Boldly Innovating to Unlock the Full Potential of Genetic Medicines for Millions of Patients

Leading Clinical Stage Next Generation AAV Company

PROVEN Platform

DIRECTED EVOLUTION: ~1B VECTOR SEQUENCES
Nobel Prize-Winning Technology

NEXT GENERATION
Vector Discovery & Payload Design

ROBUST Product Engine

MODULAR
Gene Delivery Vectors

4 THERAPEUTIC AREAS

3 ROUTES OF ADMIN
Intravitreal
Aerosol
Intravenous

STRONG Clinical Data

4D-150 BROAD PROOF-OF-CONCEPT
Potential Best-in-Class Safety Enabling Development in Broad Wet AMD Patient Population

4D-710 & 4D-310
Demonstrated Promising Transduction & Early Clinical Signals

LATE-STAGE Capabilities

WORLD CLASS SENIOR RETINA TEAM
Six Approvals & Five Launches of Major Products

GMP MFG EXPERTISE
Hybrid & De-Risked

COMMERCIAL
Development Strategy for Transformational Products in Large Markets

$551M cash* as of September 30, 2024; Runway through H1 2027

*Includes cash equivalents and marketable securities (unaudited)

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

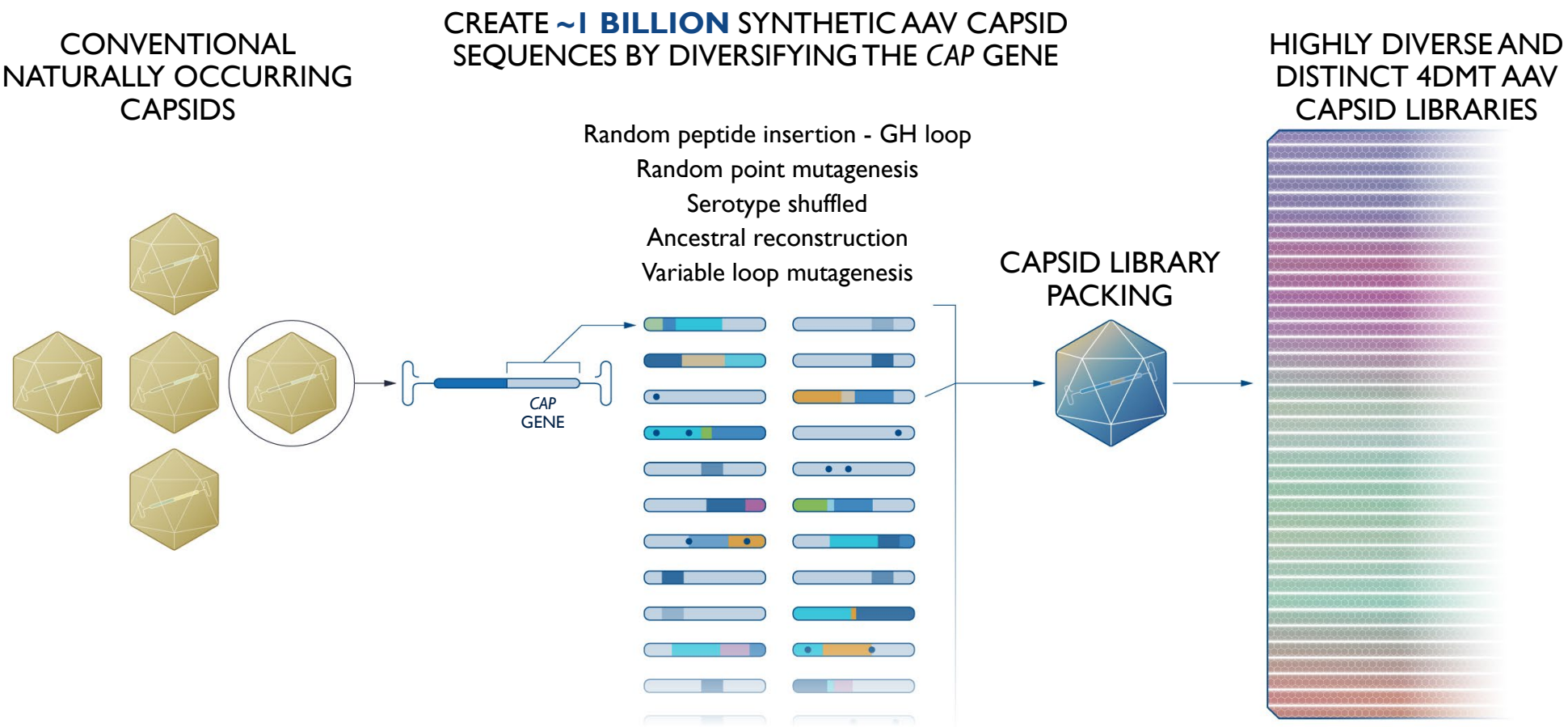
- Limited Delivery
- Limited Transduction
- Increased Inflammation and Toxicity
- Vulnerability to Neutralizing Antibodies

Narrow Focus on Niche Diseases

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

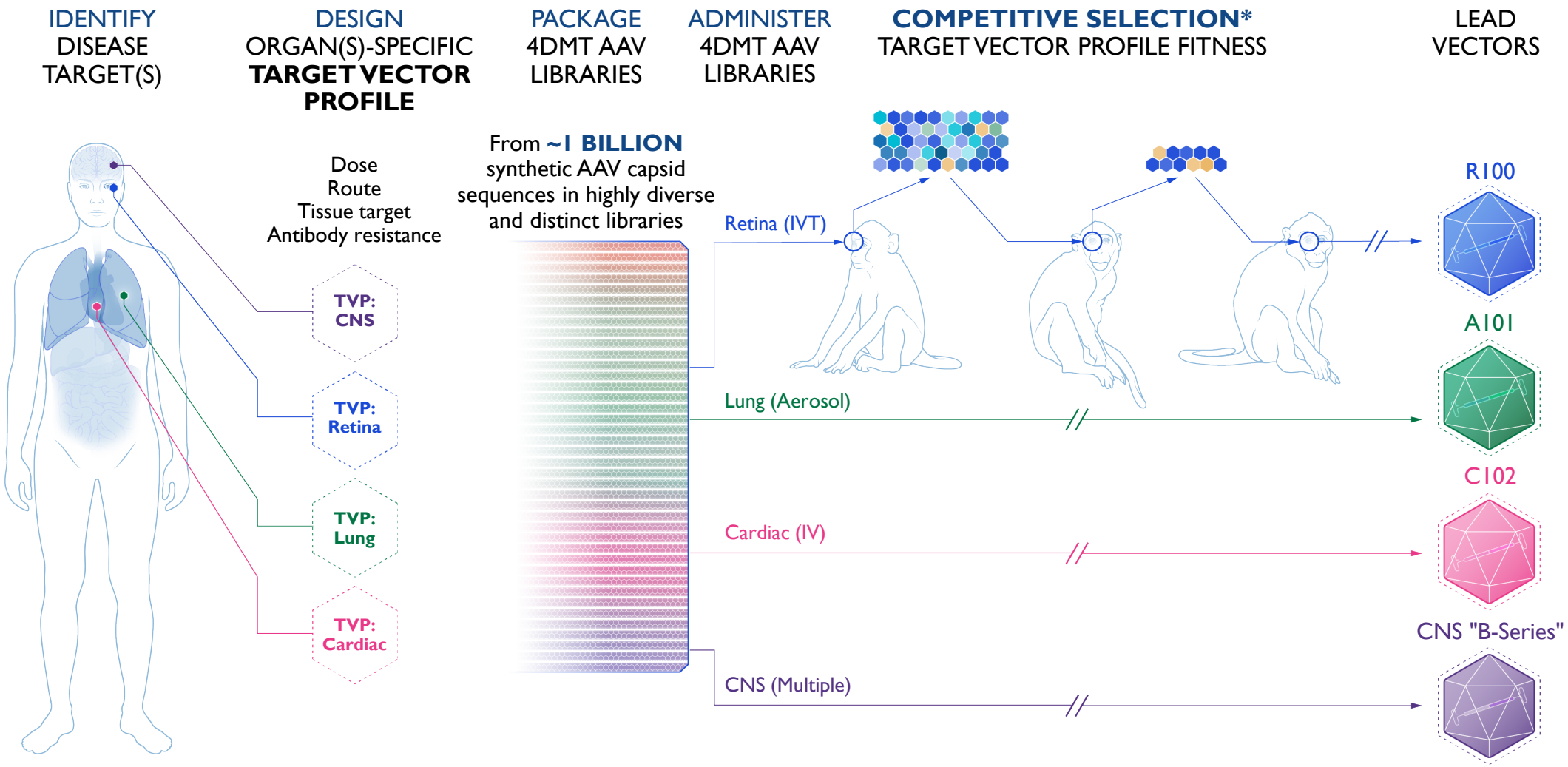
Platform Solution: ~1 Billion Synthetic Capsid Sequences

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

Large Market Ophthalmology

Modular Vector: R100

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

World Class Senior Ophthalmology Leadership Team:

100+ Years of Experience with Six Approvals & Five Launches of Major Products

Robert Kim, MD

Chief Medical Officer

30+ years

Clinical Science, Clinical Operations, Early- & Late-stage Clinical Development

Genentech — A Member of the Roche Group
NOVARTIS
Apellis
gsk
LUCENTIS RANIBIZUMAB INJECTION
SYFOVRE (pegcetacoplan injection)
Beovu (brolucizumab-dbll) Injection

Dhaval Desai, PharmD

Chief Development Officer

20+ years

Late-stage Product Development, Medical Affairs & Scientific Communications

IVERIC BIO An Astellas Company
NOVARTIS
izervay (avacincaptad pegol intravitreal solution) 2 mg
Beovu (brolucizumab-dbll) Injection

Christopher Simms

Chief Commercial Officer

25+ years

Pre-commercial & Commercial, Pre-launch Preparations & Development

IVERIC BIO An Astellas Company
NOVARTIS
Genentech — A Member of the Roche Group
izervay (avacincaptad pegol intravitreal solution) 2 mg
Beovu (brolucizumab-dbll) Injection
LUCENTIS RANIBIZUMAB INJECTION

Carlos Quezada-Ruiz, MD, FASRS

SVP, Therapeutic Area Head, Ophthalmology

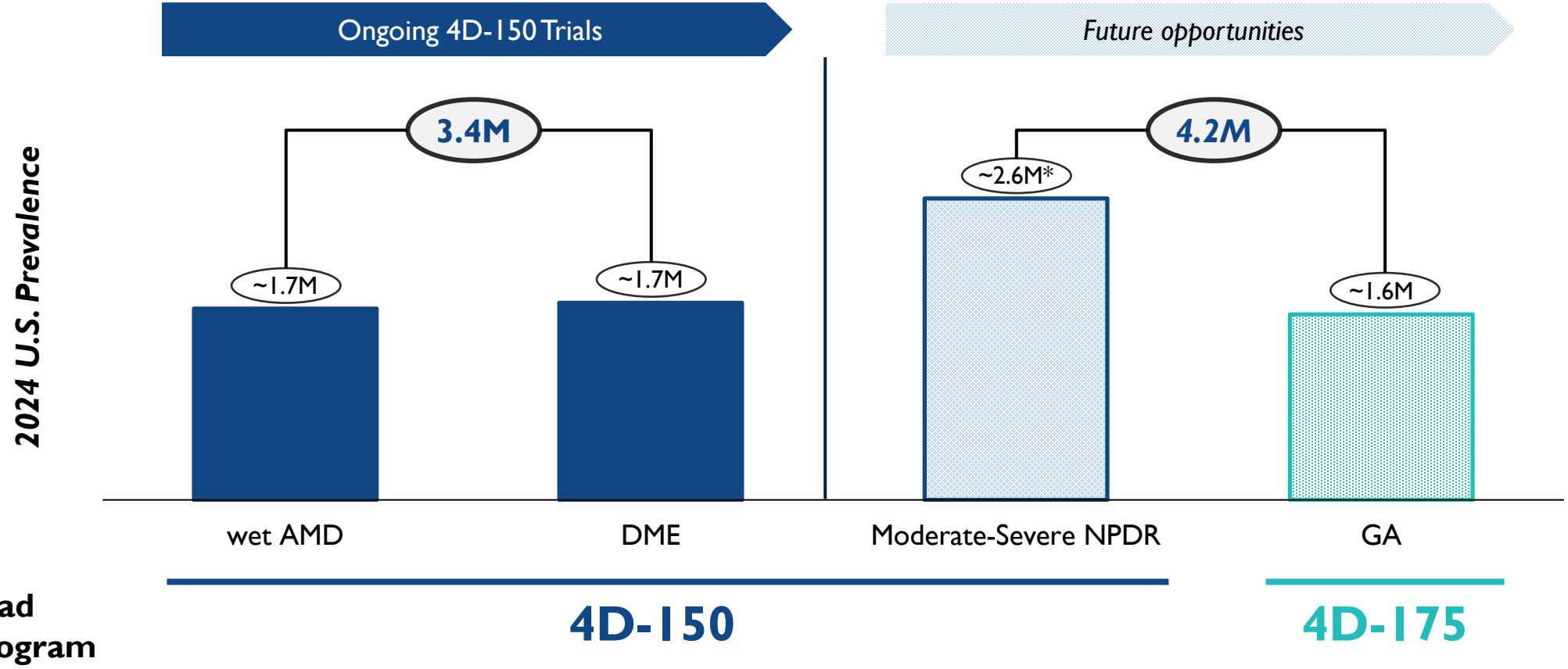
20+ years

Leads Ophthalmology R&D, Early- & Late-stage Clinical Development

Genentech — A Member of the Roche Group
Roche
VABYSMO faricimab-svoa injection 6 mg
susvimo ranibizumab injection 100 mg/mL For Ocular Implant
LUCENTIS RANIBIZUMAB INJECTION

Wet AMD is the First of Four Large Market Retina Indications for 4DMT

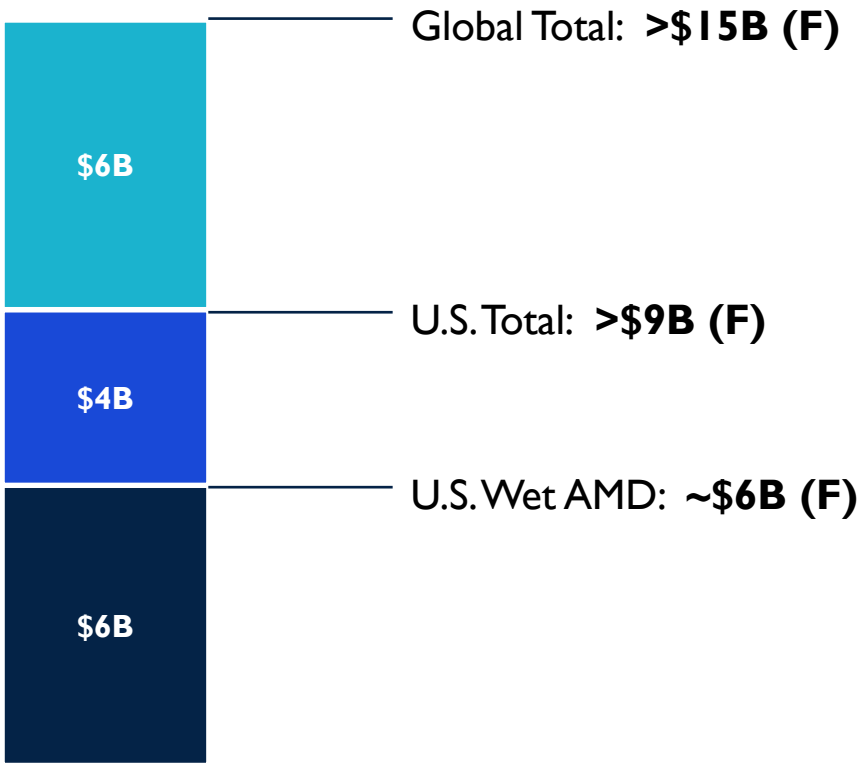
~7.6 Million Patients in U.S.



Market Scope 2023 Retinal Pharmaceuticals Market Report, published Aug 2023. * Excludes patients with DME.

U.S. Wet AMD Market is ~$6B Today and Will Continue to Grow

2024 Branded Ocular Anti-VEGF Market



Wet AMD Population Estimates (U.S., 2024)

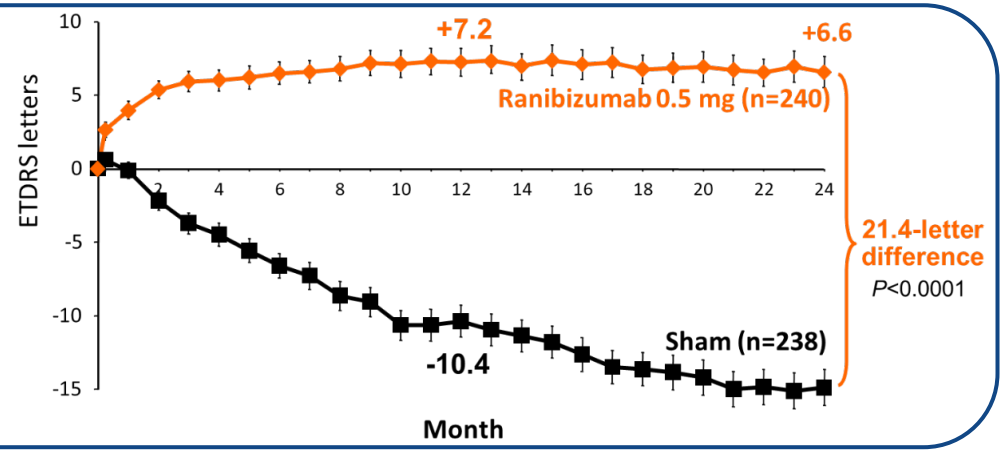
1.65M	Prevalence
>200K	Annual Incidence
~3%	Population Growth (65+)

Sources: For anti-VEGF market - GlobalData, GrandView Research.
Annual incidence derived from analysis of key publications (Vanderbeek 2011, Rudnicka 2015, Klein 2011 and Fisher 2016), triangulated with IQVIA claims data; population growth calculated from U.S. census projections for ages 65+ in the U.S.
Prevalence sourced from Marketscope Retina Market Report 2023; (F) = forecast for 2024

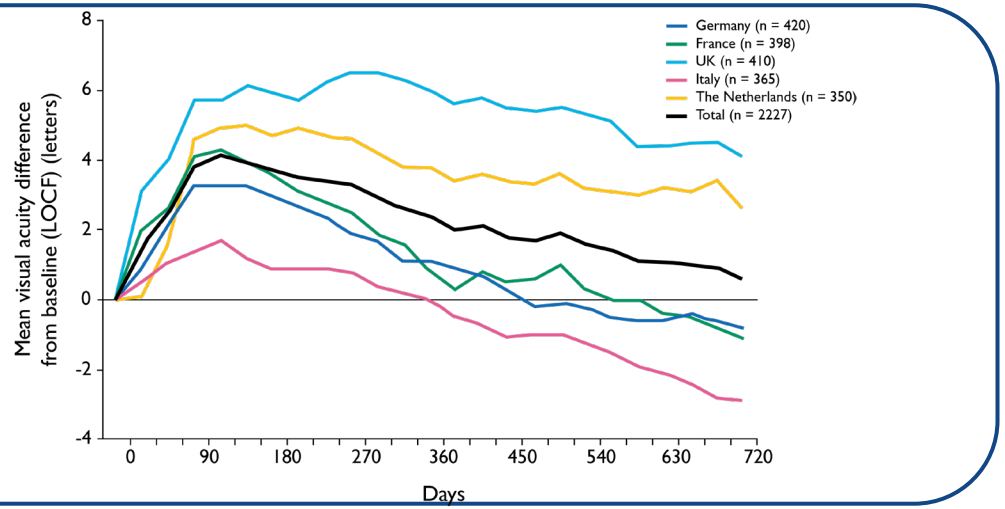
Wet AMD is Still a Major Cause of Vision Impairment & Blindness[1] Despite the Introduction of Anti-VEGF Therapies >15 Years Ago[2]

- Wet AMD, diabetic macular edema, and diabetic retinopathy are among the **leading causes of moderate or severe vision impairment**
- Most patients in the real world **fail to achieve & maintain visual gains** seen in clinical trials
- **Major limitation of standard of care is durability**

MARINA: Frequent & Consistent Dosing Required to Maximize Vision Outcomes



AURA[3]: Infrequent & Inconsistent Dosing in the Real World Results in Loss of Initial Vision Gains

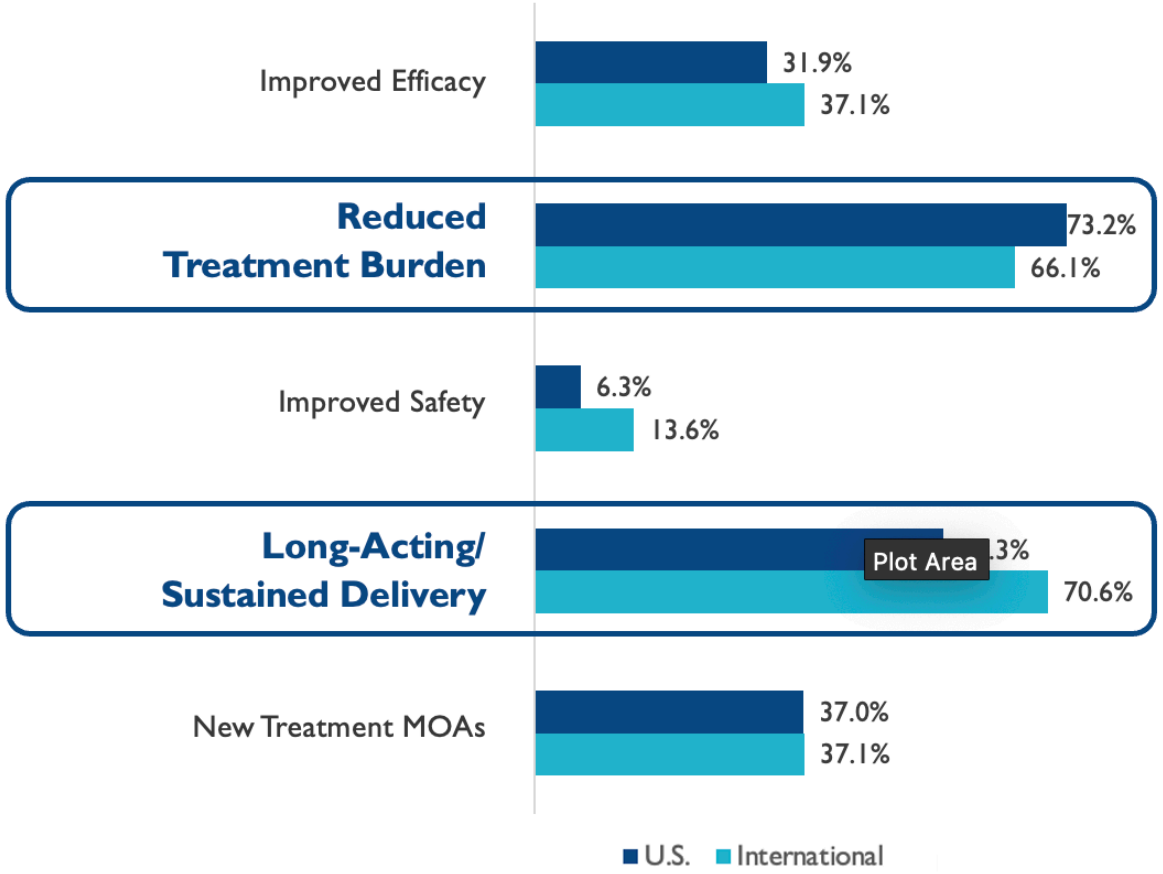


1. Burton MJ, Ramke J, Marques AP, Bourne RR, Congdon N, Jones I, et al. The Lancet Global Health commission on Global Eye Health: vision beyond 2020. *Lancet Glob Health*. 2021; 9(4):e489–e551. 2. Rosenfeld PJ et al., *N Engl J Med* 2006;355:1419-31. 3. Holz FG et al. *Br J Ophthalmol* 2015;99:220-226

Largest Unmet Need in Wet AMD is Durable Efficacy with a Safe Treatment, Despite Recent Approvals of 2nd Generation Anti-VEGFs

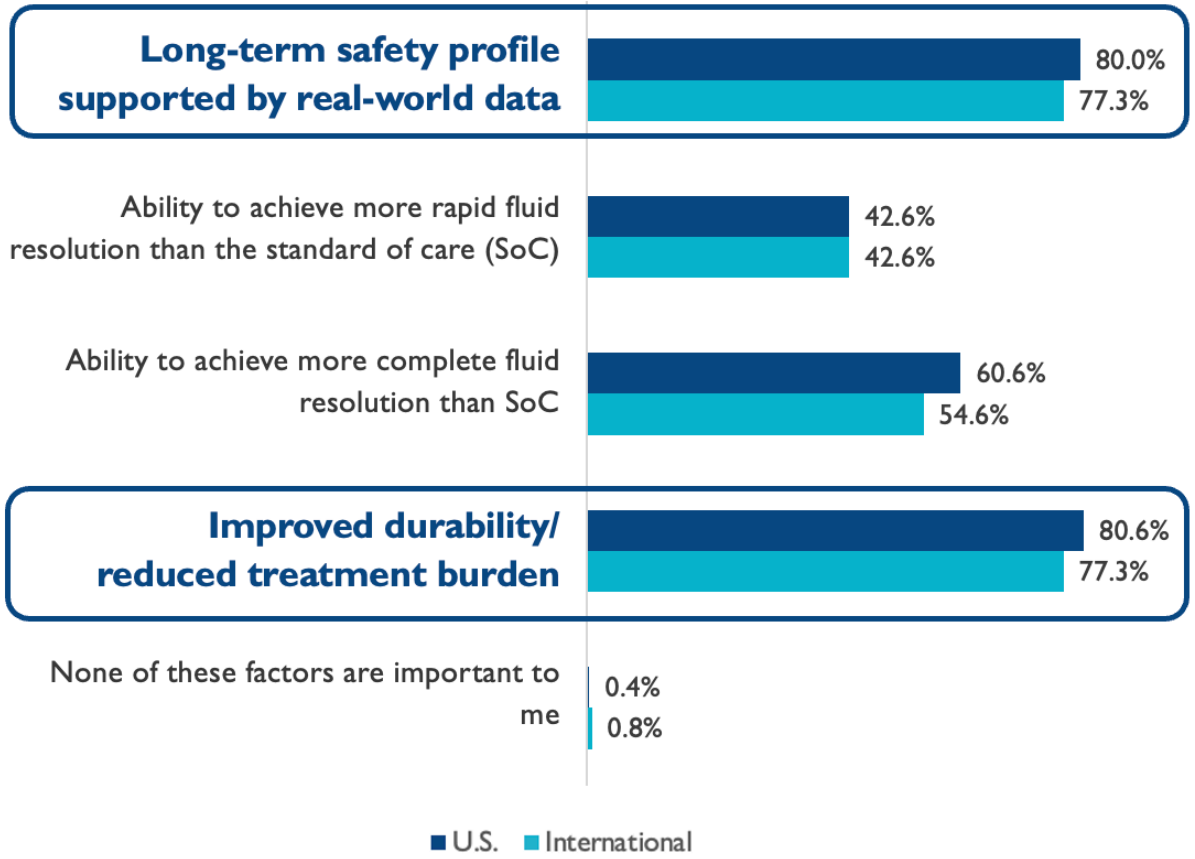
ASRS PAT Survey **2018**[1]

What are the greatest unmet needs regarding wet AMD treatment?



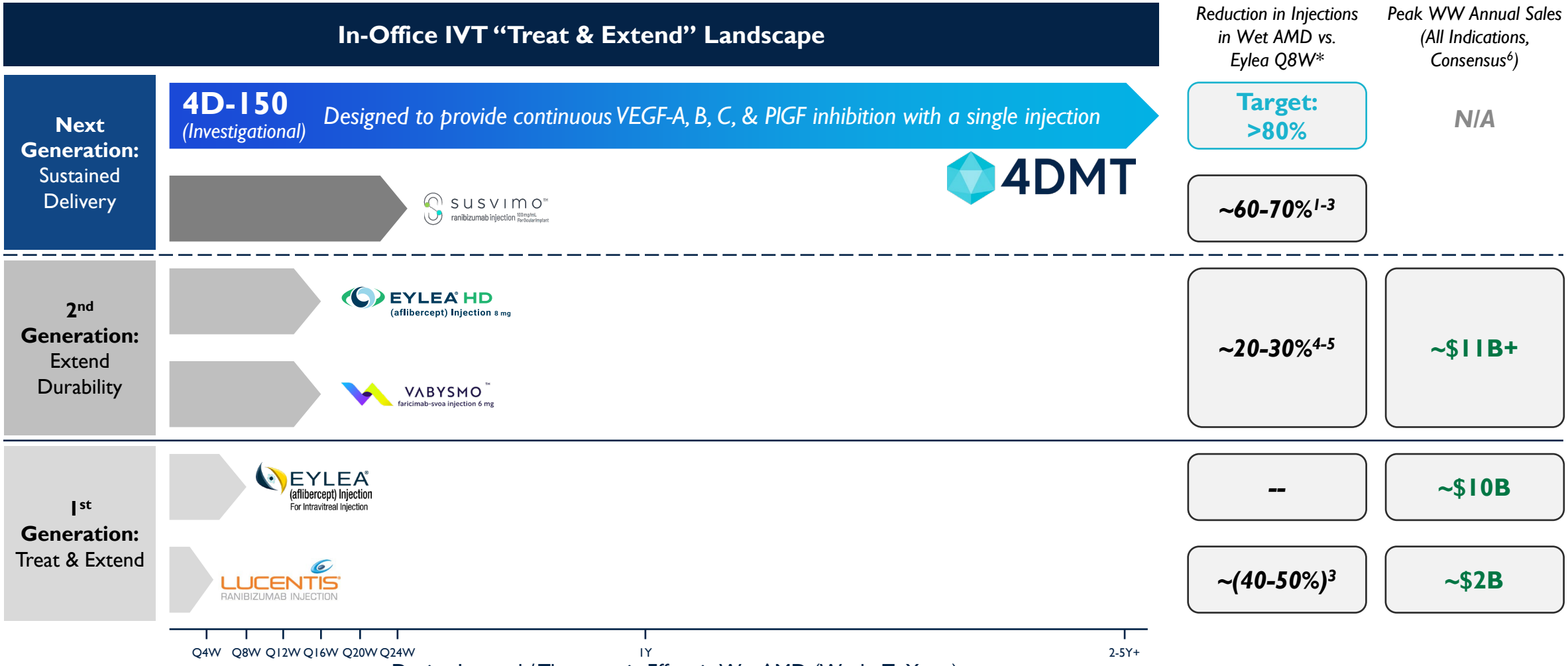
ASRS PAT Survey **2024**[2]

Which factors are most important to you when selecting anti-VEGF agent?



1. Stone TW, ed. ASRS 2018 PAT Survey. 2. Han P, ASRS 2024 PAT Survey.
PAT, Preferences and Trends.

Products with Incremental Improvements in Durability & Reduction in Treatment Burden Have Become Commercial Blockbusters



Mean no. of injections over Year 0-2: Susvimo (ARCHWAY) vs. Eylea Q8W (VIEW 1 & 2) 2. Regillo et al. *Ophthalmology* 2023; 130:735-7 (ARCHWAY). 3. Schmidt-Erfurth et al. *Ophthalmology* 2014; 121:193-201 (VIEW 1 & 2) 4. Eylea HD: Regeneron publicly available information/company website as of 8/10/23 (PULSAR data) 5. Vabysmo: CDER statistical review; Khanani et al., *Ophthalmology* 2024; 1-13 (TENAYA and LUCERNE) 6. FactSet 2028E WW sales for Eylea HD and Vabysmo; FactSet for Eylea and Lucentis peak WW sales *The data presented above are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities and differences. The values shown in the cross-study comparisons are directional and may not be directly comparable.

Ideal Therapy to Address Key Unmet Needs

1 Favorable Safety Profile

Comparable
to approved anti-VEGF agents

LUCENTIS® RANIBIZUMAB INJECTION

EYLEA® (aflibercept) Injection For Intravitreal Injection

EYLEA® HD (aflibercept) Injection 8 mg

VABYSMO™ faricimab-svoa injection 6 mg

2 Maximize Visual Outcomes with Extended Durability

Visual gains comparable
to approved anti-VEGF agents

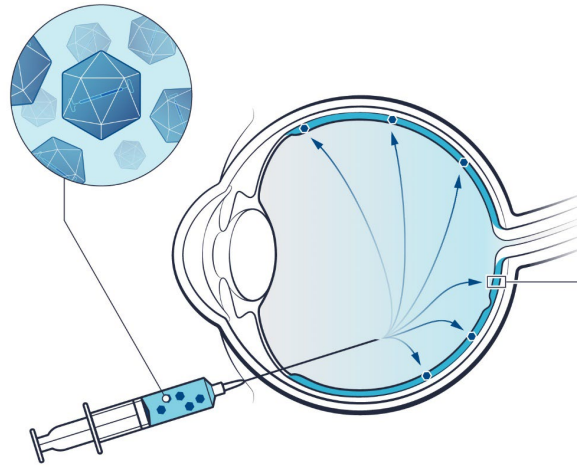
Robust reduction of overall treatment burden

Long-term durability

Potential for
extended vision preservation

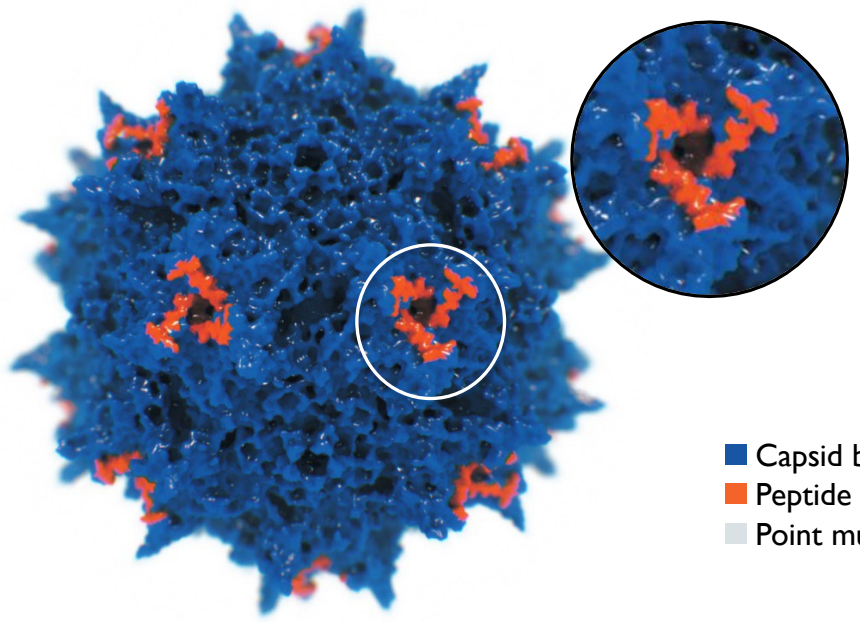
3 Route of Administration

Routine
intravitreal injection



4D-150 Designed for Sustained Intraretinal Expression of Anti-VEGF & Blockade of VEGF-C Production to Address Key Unmet Needs

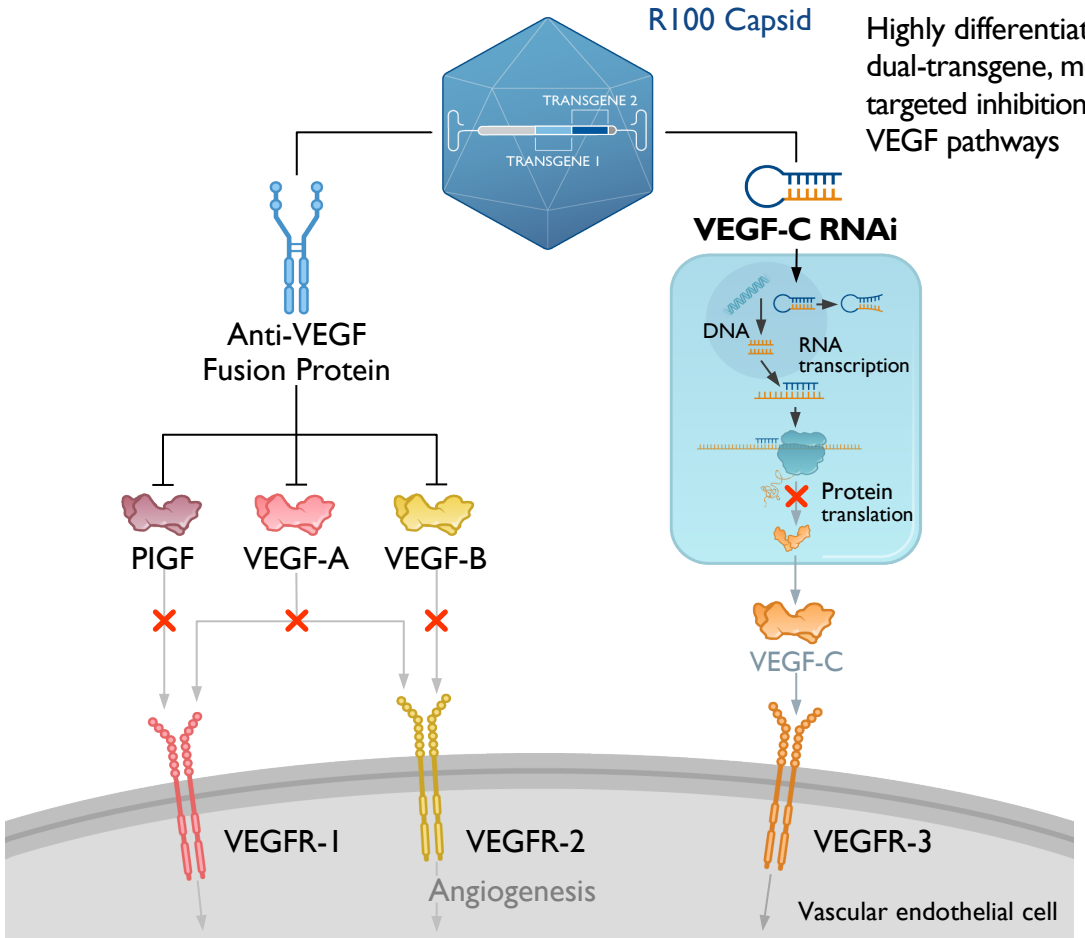
R100 Capsid



- Capsid base
- Peptide insertions
- Point mutations (internal)

- ✓ Minimal inflammation potential based on clinical data to date
- ✓ Robust delivery to multiple retinal layers
- ✓ Durable expression of transgenes

4D-150



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

Key 4D-150 Takeaways in Wet AMD

1. **Robust & Durable Clinical Activity:** Across all populations studied, including recently diagnosed patients

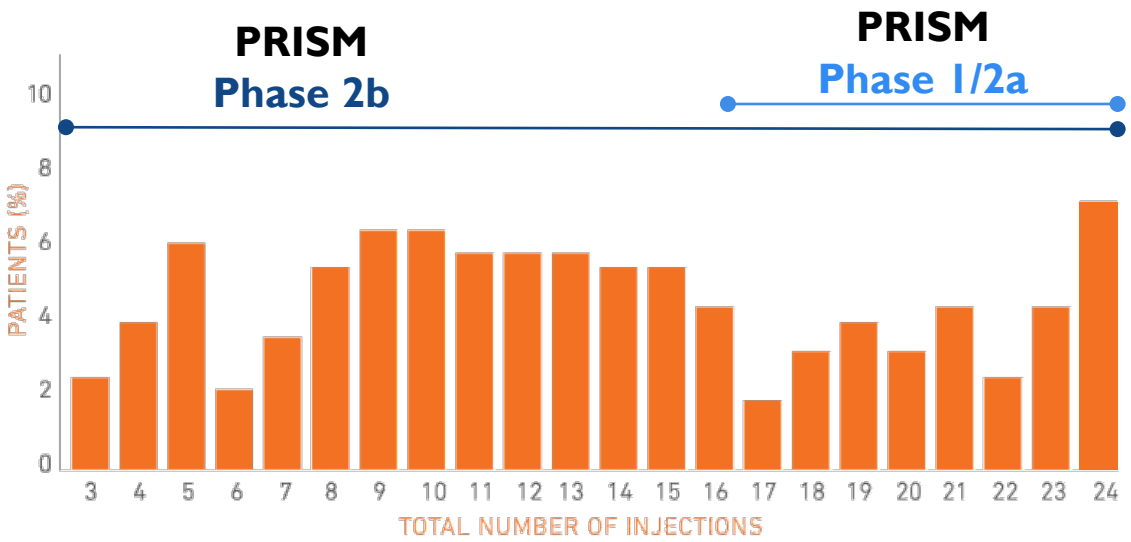
2. **Tolerability:** Well-tolerated with profile comparable to approved anti-VEGF agents

3. **4FRONT Phase 3 Design:** Maximizes probabilities of clinical, regulatory & commercial success

Data cutoff (clinical activity data), September 3, 2024.
Data cutoff (safety data), August 23, 2024.

Treatment Need in Wet AMD Population is Heterogeneous: Development Moved From Highest Need to a Broad Need Population

Lucentis HARBOR Study*



*Data on PRN ("as needed") injections received after 3 loading doses demonstrates a **high degree of heterogeneity in anti-VEGF needs in patients with wet AMD** (N=232)*

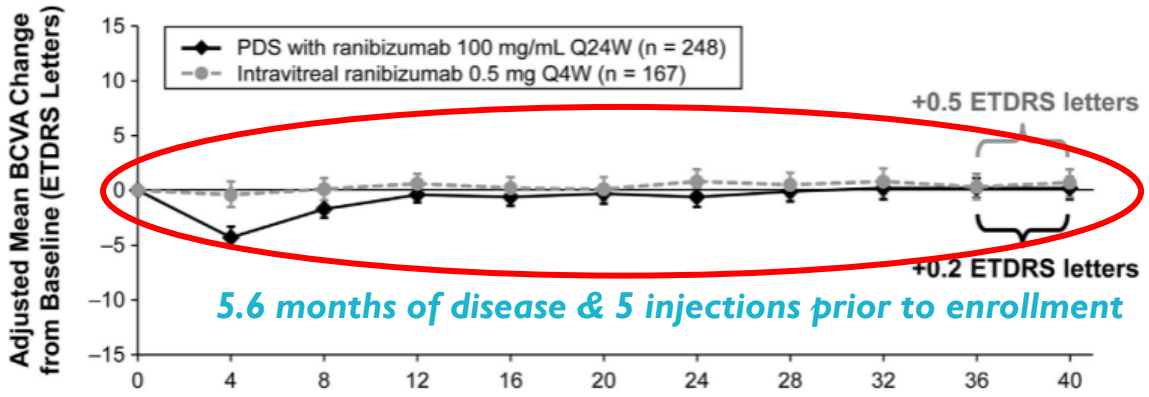
PRISM

- **Phase 1/2a: Severe Population**
  - Objectives: Safety, clinical POC
  - Enrolled: Highest anti-VEGF need & most severe disease activity population with long disease duration
- **Phase 2b: Broad Population**
  - Objectives: Efficacy, Phase 3 dose & population
  - Enrolled: Broad range of patients with variable anti-VEGF need, disease severity & disease duration

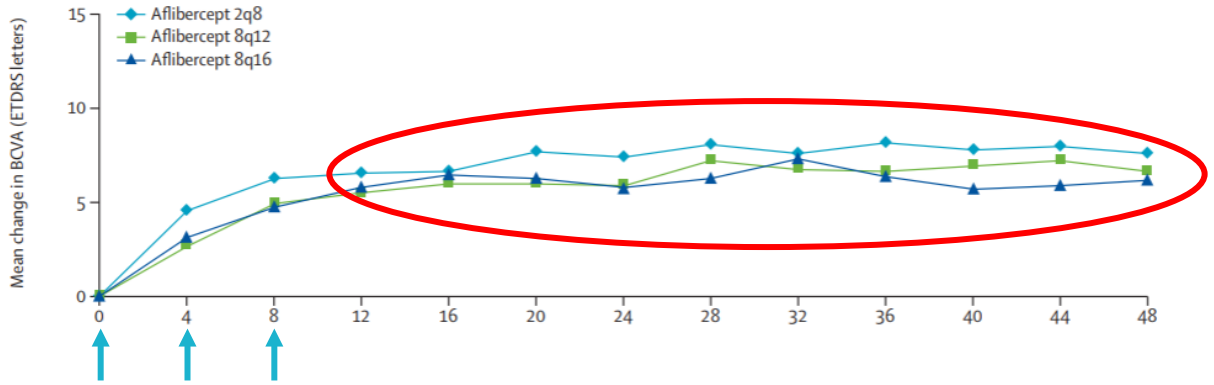
*Lucentis.com

Initial Vision Gains Achieved by **First 3 Loading Injections:** Objective of 4D-150 Sustained Delivery is to **Maintain Disease**

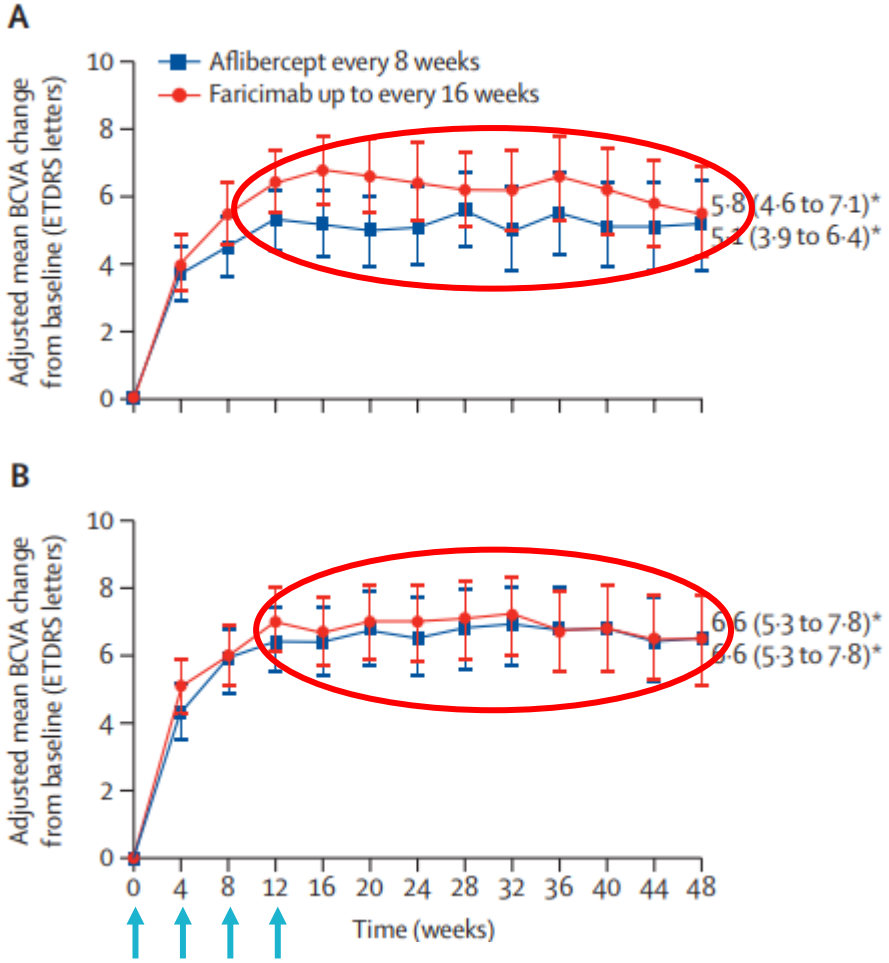
ARCHWAY (SUSVIMO)



PULSAR (EYLEA HD)

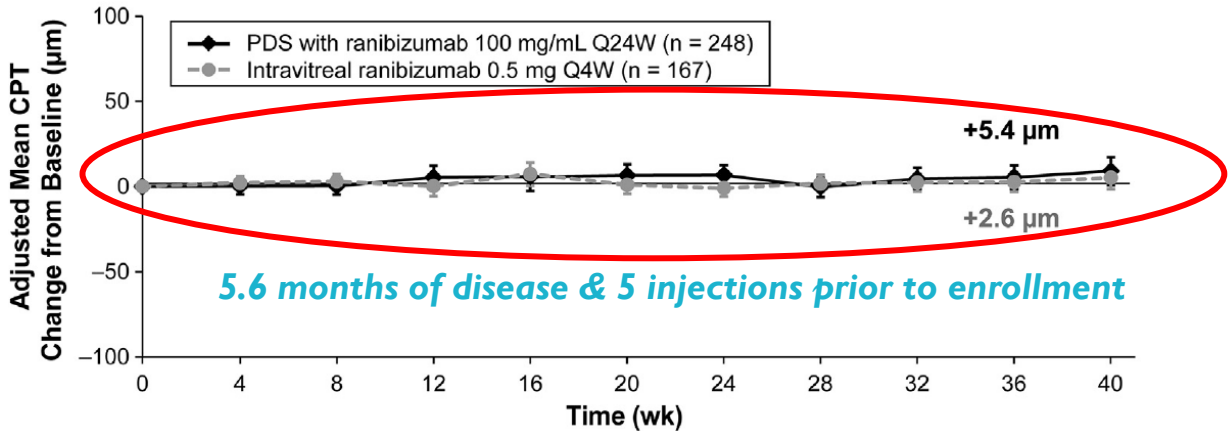


TENAYA / LUCERNE (VABYSMO)

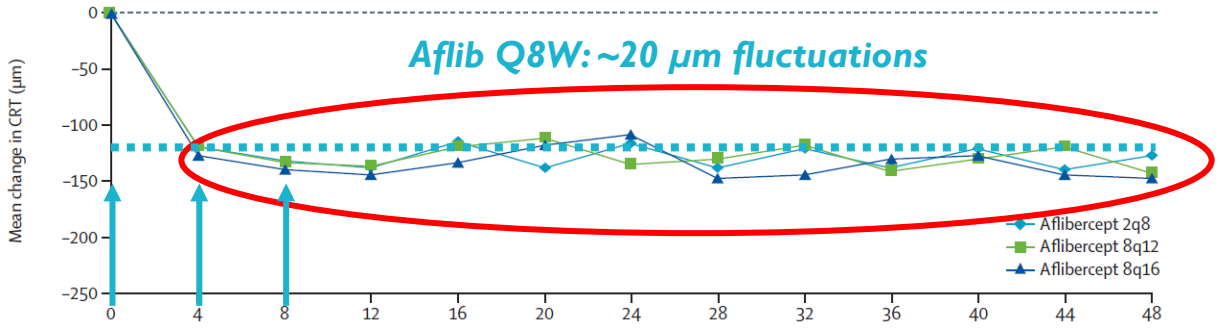


Initial CST Decline Achieved by **First Loading Injection:** Objective of 4D-150 Sustained Delivery is to **Maintain Disease**

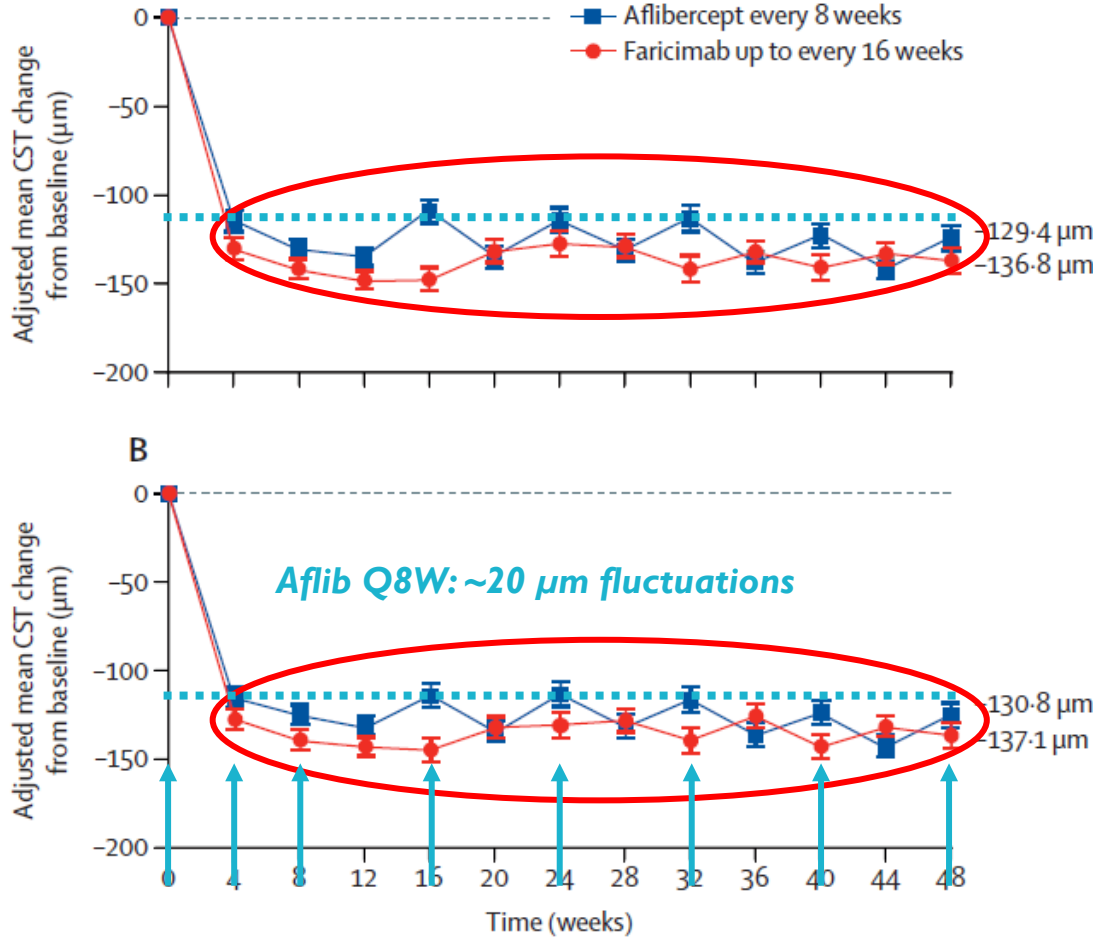
ARCHWAY (SUSVIMO)



PULSAR (EYLEA HD)



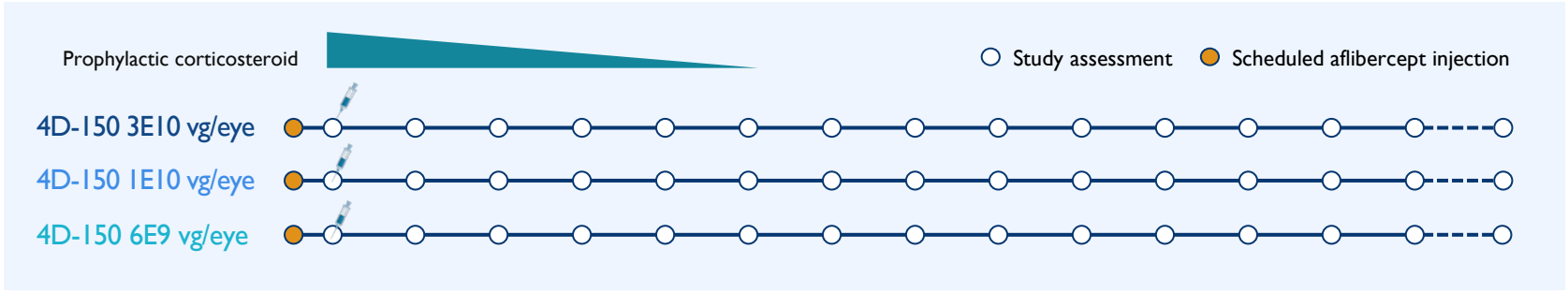
TENAYA / LUCERNE (VABYSMO)



1. Holekamp NM et al. *Ophthalmol* 2022; 129(3):295-307 (ARCHWAY); 2. Lanzetta P et al. *Lancet* 2024; 403:1141–52 (PULSAR); 3. Khanani A et al. *Ophthalmol* 2024; 131(8):914-26 (TENAYA & LUCERNE)

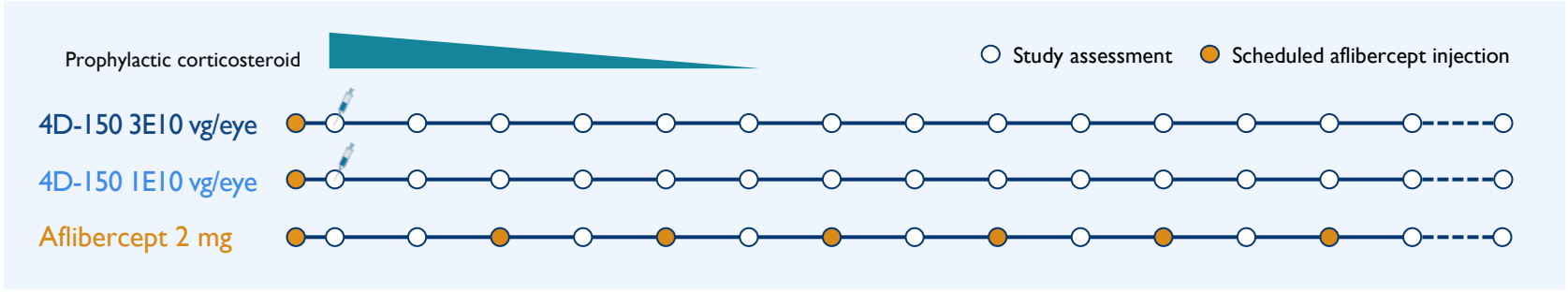
4D-150 Phase 1/2 Wet AMD Development Plan Included Recently Diagnosed Patients in Phase 2b

Phase 1
Dose Exploration



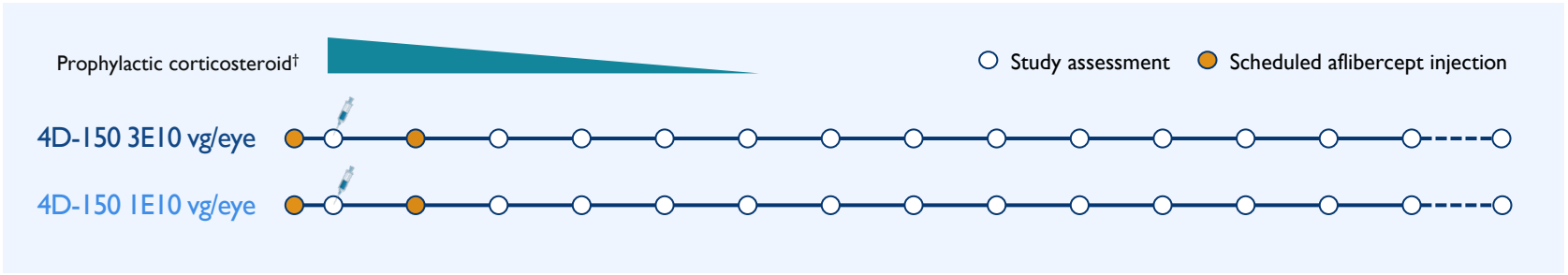
Population Characteristics*
BCVA: 65 letters
CST: 392 µm
Injections (prior year): 9.3
Recently Diagnosed‡: **0%**
Time since Dx: 3.6 years

Phase 2a
Dose Expansion (randomized 2:2:1)



Population Characteristics*
BCVA: 70 letters
CST: 442 µm
Injections (prior year): 9.6
Recently Diagnosed‡: **0%**
Time since Dx: 3.1 years

Phase 2b
Population Extension



Population Characteristics*
BCVA: 72 letters
CST: 329 µm
Injections (prior year): 4.4
Recently Diagnosed‡: **60%**
Time since Dx: 1.4 years

Week: –1 0 4 8 12 16 20 24 28 32 36 40 44 48 52 … 104

*Mean values unless otherwise indicated, All doses. †Participants received either difluprednate ophthalmic emulsion, triamcinolone acetonide with prednisolone taper, or dexamethasone. ‡Defined as ≤6 months since diagnosis at screening.

PRISM Population Compared to Recent Phase 3 IVT Wet AMD Studies

Asset	Study	Population	Mean time since Dx	Mean CST	Mean number of injections in previous year	Number of Loading Doses
EYLEA	VIEW1/2	**Treatment Naïve**	NA	313-342 µm	0	3
BEOVU	HAWK/HARRIER	**Treatment Naïve**	NA	360-370 µm	0	3
VABYSMO	TENAYA/LUCERNE	**Treatment Naïve**	67-74% within 1 month	350-360 µm	0	4
EYLEA HD	PULSAR	**Treatment Naïve**	NA	370 µm	0	3
SUSVIMO	Archway	**Previously Treated**	5.6 months	177 µm (CPT)	5	0*
4D-150 Ph1/2a (3E10)	**PRISM**	**Previously Treated**	**3.7 years**	**425 µm**	**10.2**	**1**
4D-150 Ph1/2a (AFLB)	**PRISM**	**Previously Treated**	**2.1 years**	**419 µm**	**9.3**	**1**
4D-150 Ph2b (3E10)	**PRISM**	**Previously Treated**	**1.8 years**	**336 µm**	**4.4**	**2**

1. Heier JS et al. *Ophthalmol* 2012; 119(12):2537-48 (VIEW 1 & 2) 2. Dugel PU et al. *Ophthalmol* 2020; 127:72-84 (HAWK & HARRIER) 3. Khanani A et al. *Ophthalmol* 2024; 131(8):914-26 (TENAYA & LUCERNE) 4. Lanzetta P et al. *Lancet* 2024; 403:1141–52 (PULSAR) 5. Holekamp NM et al. *Ophthalmol* 2022; 129(3):295-307 (ARCHWAY)

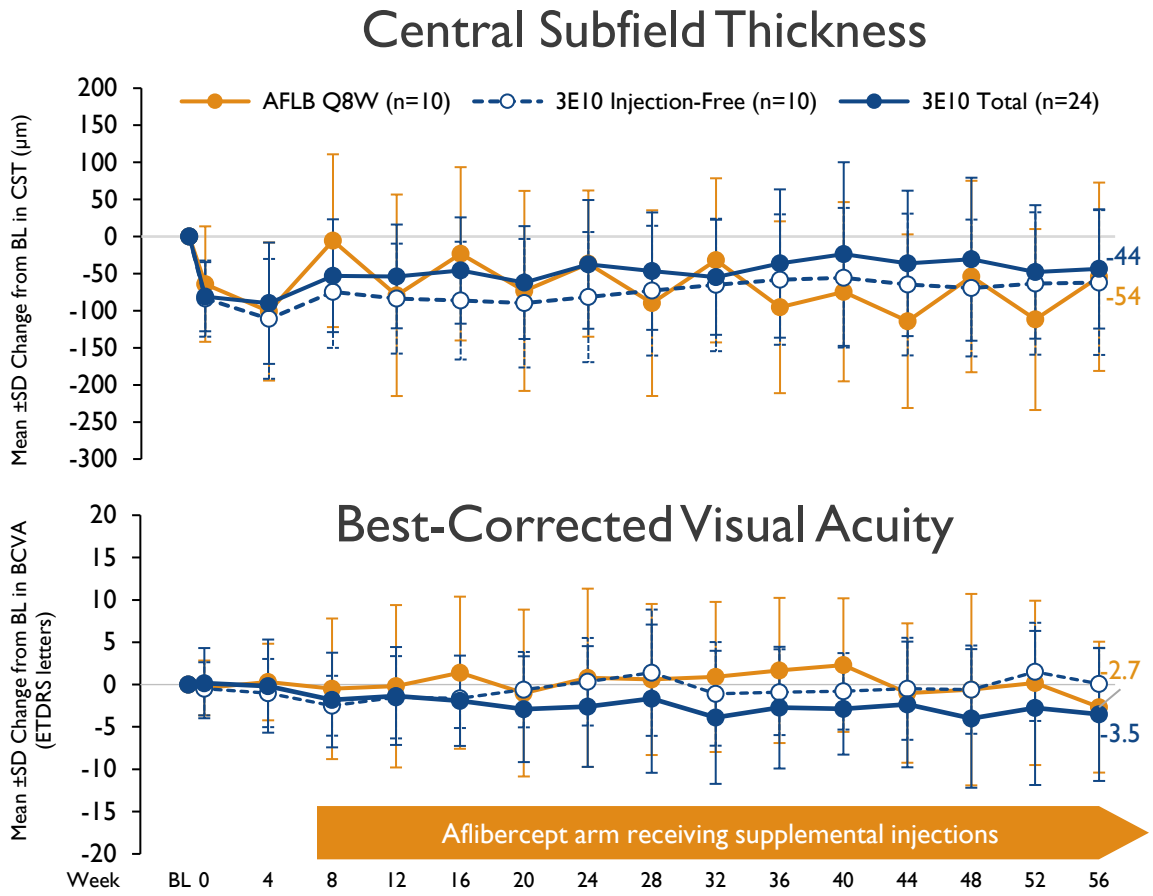
Wet AMD Population Matters:
Comprehensive Phase 1/2 Program Studied Broad Range of Disease Severity

Cohort	Phase 1/2a (Dose Exploration & Expansion)	Phase 2b (Population Extension)	Phase 2b Subgroup (Population Extension)
Population	**Severe** ~10 prior injections L12M >400 µm mean CST	**Broad** ~4-5 prior injections L12M <350 µm mean CST	**Recently Diagnosed** ~3 prior injections L12M ~300 µm mean CST

4D-150 vs. Aflibercept in Severe Patients (Phase 1/2a)

Visual Acuity & Anatomy Comparable to Q8W AFLB 2mg with Robust Reduction in Treatment Burden

Anatomy & Visual Acuity 4D-150 vs. Aflibercept

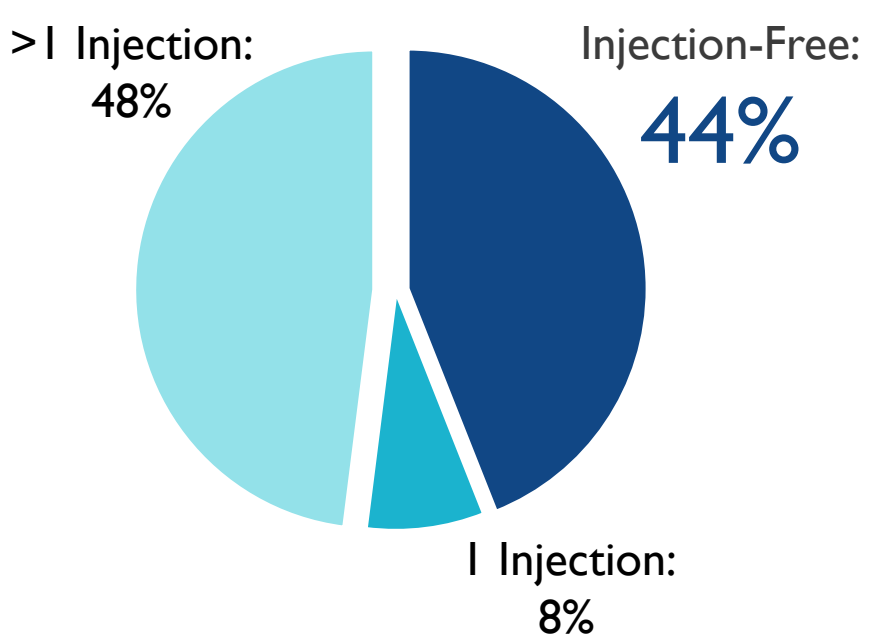


Treatment Burden Post-4D-150 Through Year 1 (KM Est.)

4D-150
3E10 vg/eye

~10 injections in 12 mos. prior to study entry

>400 µm mean CST



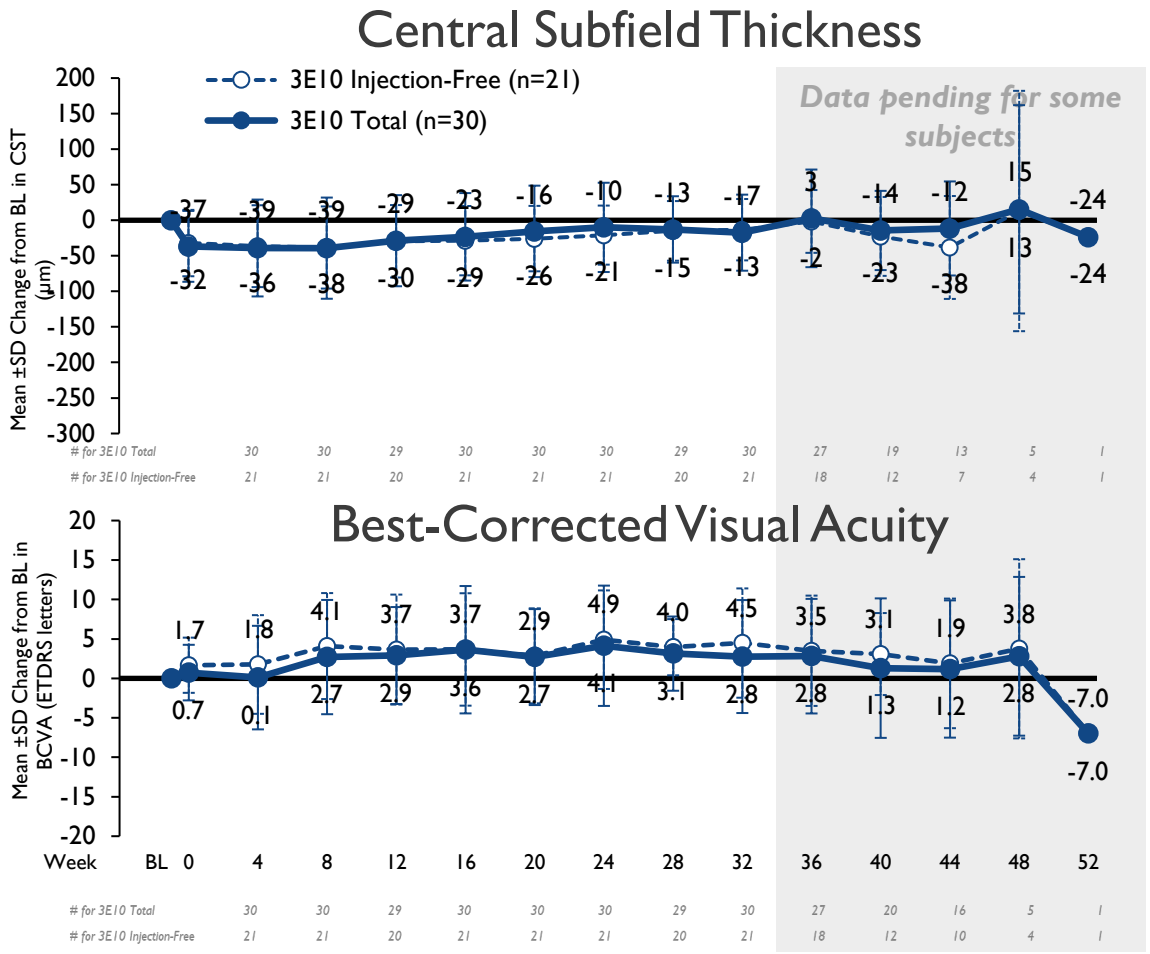
Overall Treatment Burden Reduction:

83%

4D-150 in Broad Population (Phase 2b)

Visual Acuity & Anatomy Stable with Robust Reduction in Treatment Burden

Anatomy & Visual Acuity 4D-150

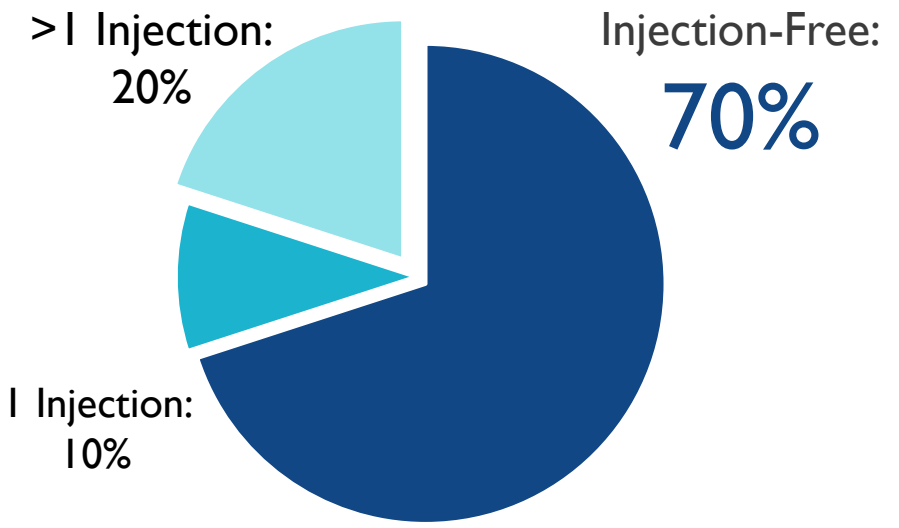


Treatment Burden Post-4D-150 Through Year 1 (KM Est.)

4D-150
3E10 vg/eye

~4-5 injections in 12 mos. prior to study entry

<350 µm mean CST



Overall Treatment Burden Reduction:

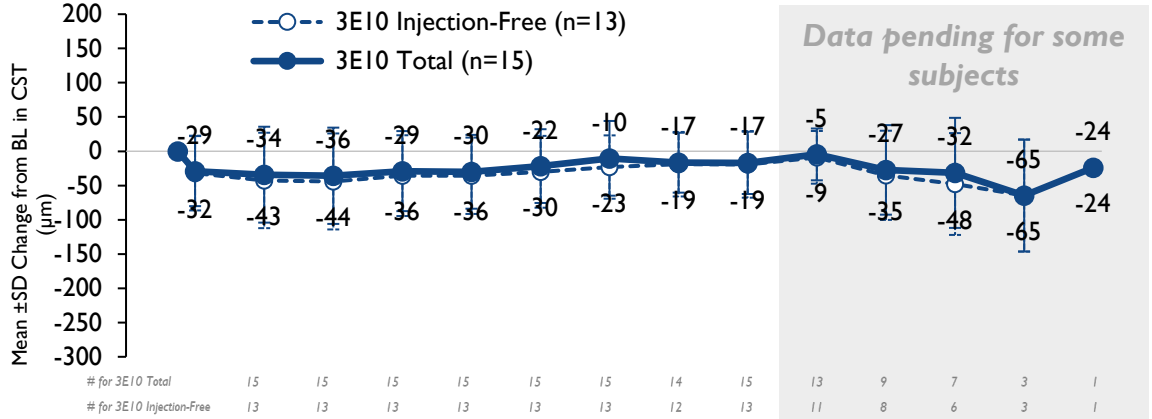
89%

4D-150 in Recently Diagnosed (≤6 Months) Population from Phase 2b

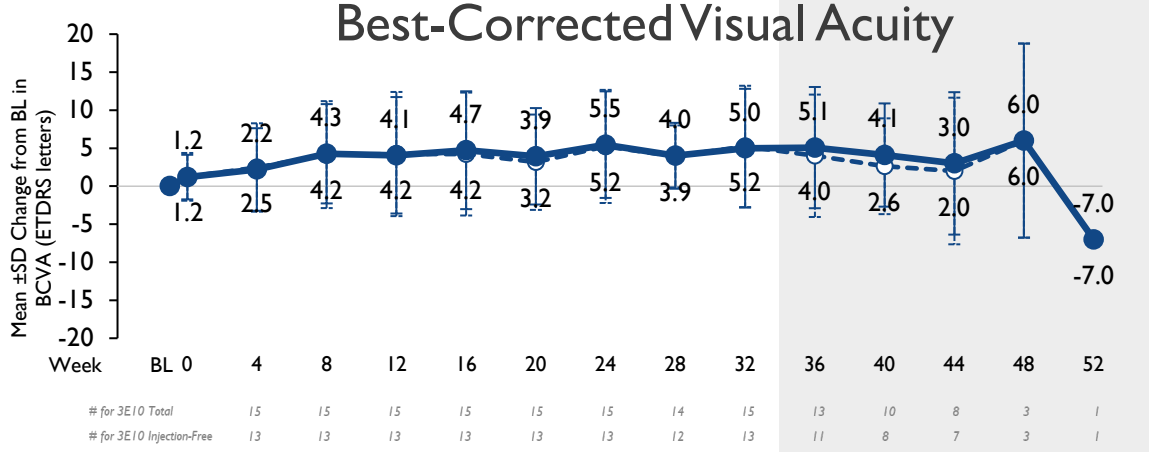
Visual Acuity & Anatomy Stable With Robust Reduction in Treatment Burden

Anatomy & Visual Acuity 4D-150

Central Subfield Thickness



Best-Corrected Visual Acuity

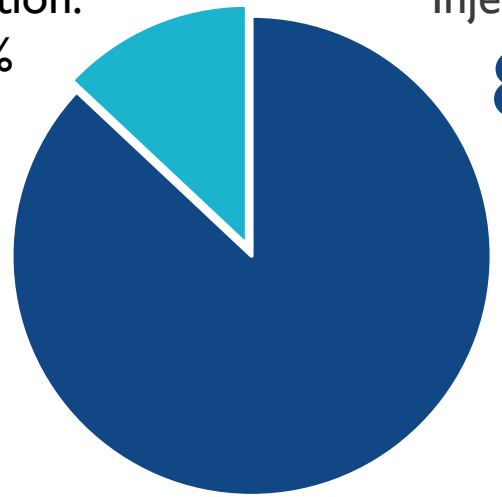


Treatment Burden Post-4D-150 Through Year 1 (KM Est.)

4D-150
3E10 vg/eye

~3 injections in 12 mos. prior to study entry

~300 µm mean CST



Overall Treatment Burden Reduction:

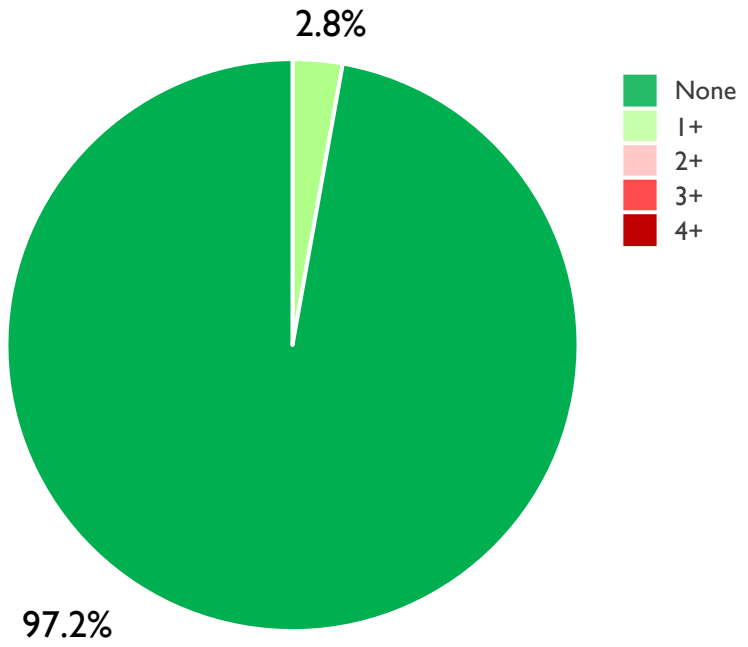
98%

4D-150 Continues to be Well Tolerated

- No 4D-150–related serious adverse events
- Rate of 3E10 dose 4D-150–related intraocular inflammation: **Wet AMD**
  - **2.8%** (2 of 71) had transient 1+VC at any timepoint
  - **99%** (70 of 71) completed steroid prophylaxis taper on schedule
- No 4D-150–related hypotony, endophthalmitis, vasculitis, choroidal effusions or retinal artery occlusions observed to date
- Rate of intraocular inflammation: **DME**
  - **0%** treated at any dose (n=22) had IOI at any timepoint

All 4D-150 3E10 vg/eye-Treated Wet AMD Patients (N=71)

*Highest SUN/NEI Score (4D-150–Related)**



Data cutoff, August 23, 2024.
*Duration of follow up, ≤2.5 years. NEI, National Eye Institute; SUN, Standardization of Uveitis Nomenclature.

4FRONT Phase 3 Program in Treatment Naïve Wet AMD Population

Design Maximizes Probabilities of Clinical, Regulatory & Commercial Success

1

Informed by:

- PRISM interim data
- Phase 3 designs of marketed intravitreal anti-VEGF products
- Regulatory discussions with FDA & EMA under RMAT & PRIME

2

Goals:

- Maximize probability of success for:
  - Primary endpoint: BCVA non-inferiority
  - Secondary endpoint: treatment burden reduction
  - Commercialization

3

Design features:

- Anti-VEGF responsive on study to be randomized
- 4D-150 3E10 vg/eye dose
- Durezol topical eyedrops
- 3 monthly loading doses applied to both arms
- Comparator arm 2Q8W dosing without supplemental injections

4FRONT-1 Phase 3 Wet AMD Study Design

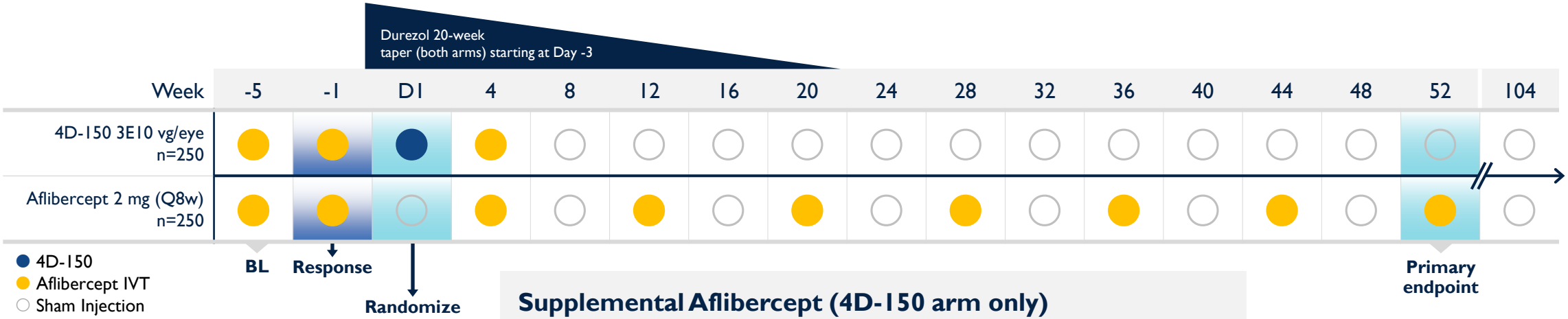
Primary Endpoint: BCVA Noninferiority of 4D-150 3E10 vg/eye to Aflibercept 2mg Q8 weeks

Key Inclusion Criteria

Treatment naïve wet AMD

BCVA:
25-78 letters

Anti-VEGF responsive:
After Week -5 loading dose



Supplemental Aflibercept (4D-150 arm only)

Reference Point:
After 3 loading doses

Pre-specified criteria for BCVA & CST worsening to maintain BCVA and **protect primary endpoint**

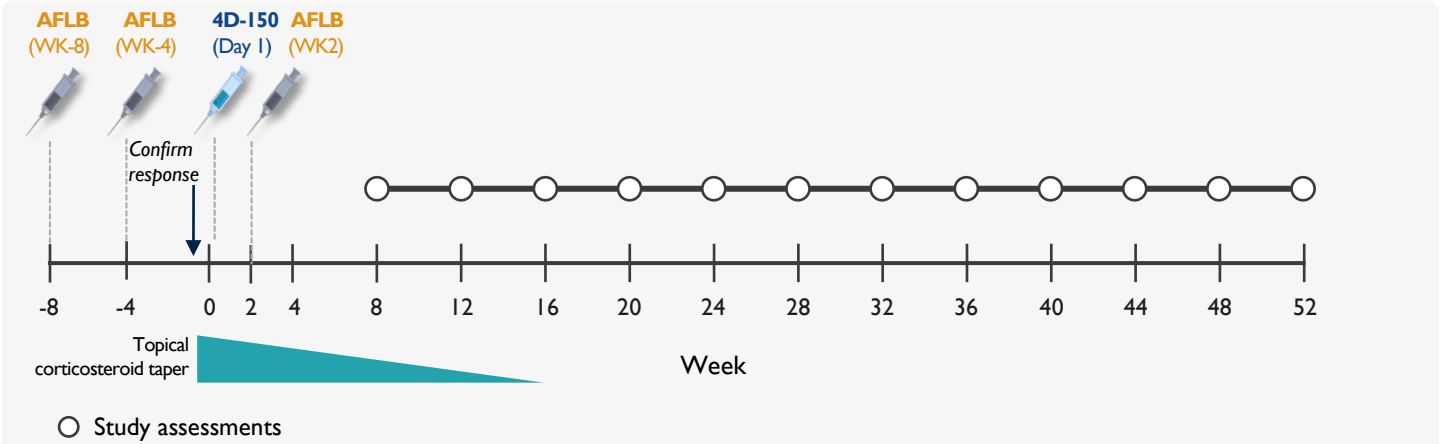
Designed to Drive Clinical, Regulatory & Commercial Success

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

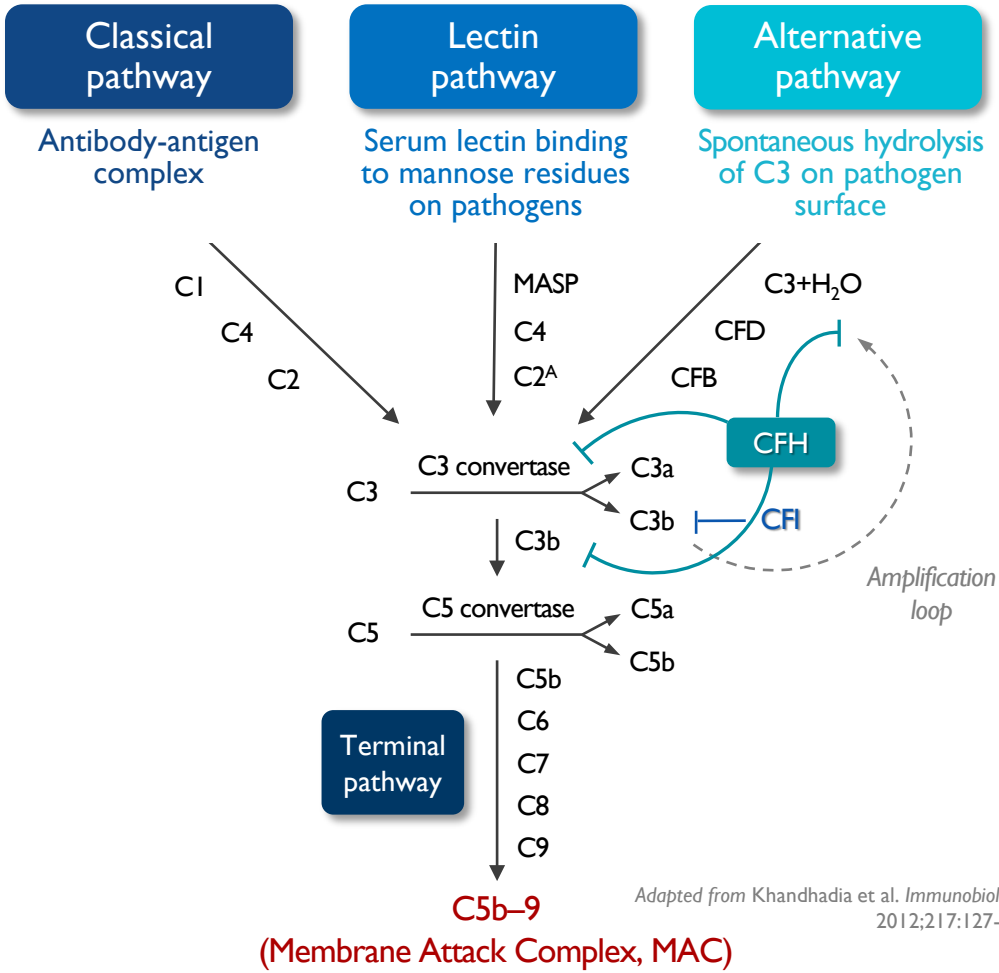
- Annualized number of aflibercept injections in the study eye

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

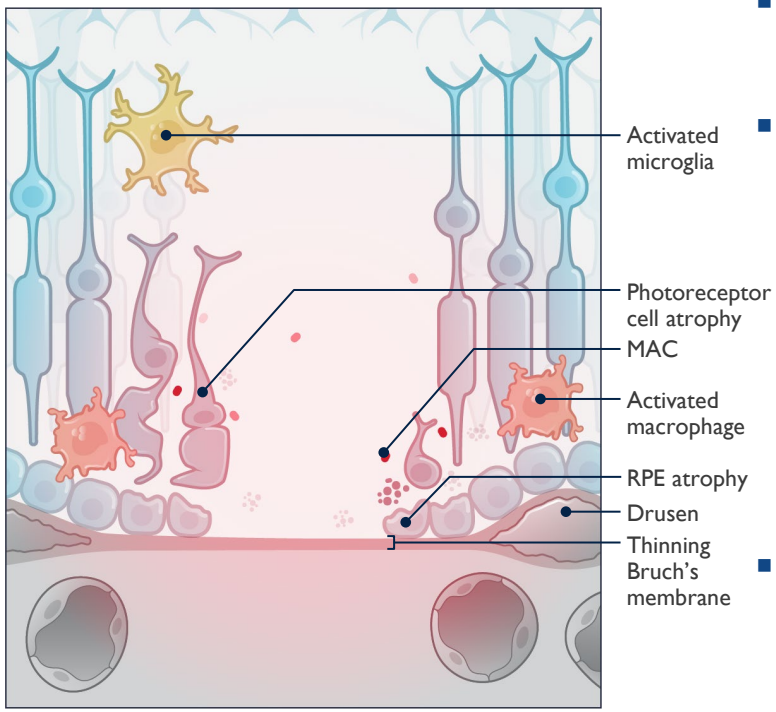
DME, Diabetic Macular Edema; BCVA, Best-Corrected visual acuity; CNV, choroidal neovascularization; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor

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%**[4] 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**[5,6]

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

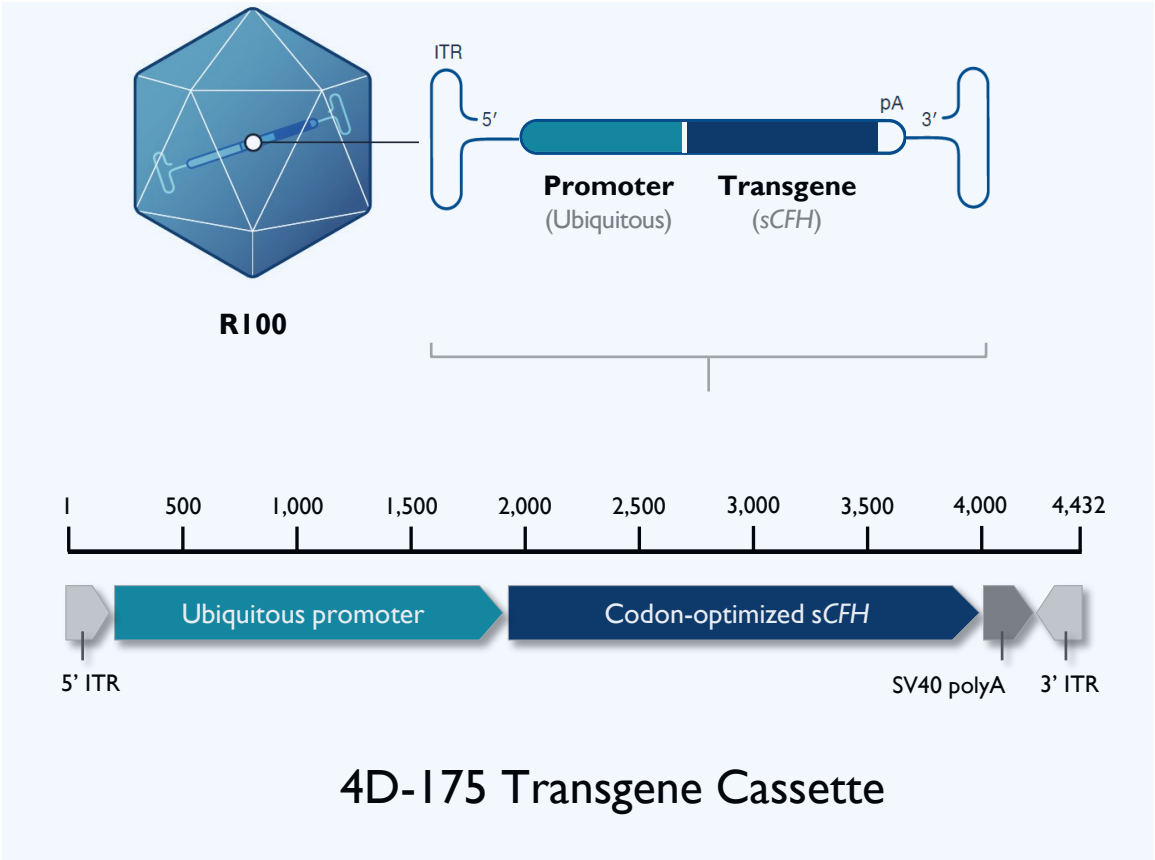
1. Rein, D. et al. *JAMA Ophthalmol.* 2022;140(12):1202-8 2. Manuelian et al. *J Clin Invest* 2003;111:1181–90. 3. Prosser et al. *J Exp Med* 2007;204:2277–83. 4. Goverdhan, S.V. et al. *Eye (Lond)* 2008; 22(6): 849-54. 5. Syfovre [package insert]. Apellis Pharmaceuticals. 6. Izervay [package insert]. 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 GAZE Dose Exploration expected to begin enrolling in Q1 2025**

4D-175: *sCFH*-Transgene Payload



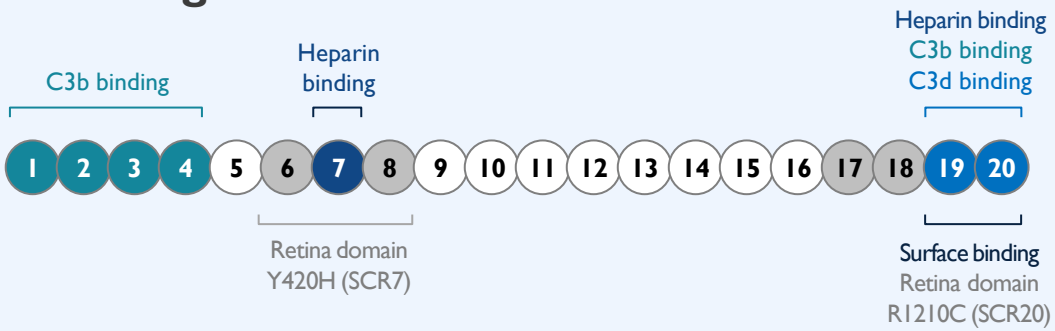
4D-175 Transgene Cassette

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]

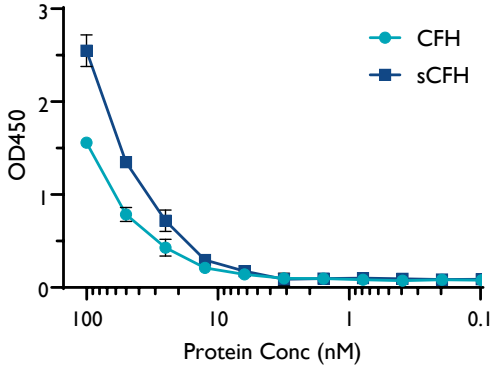


Short-form CFH (sCFH)

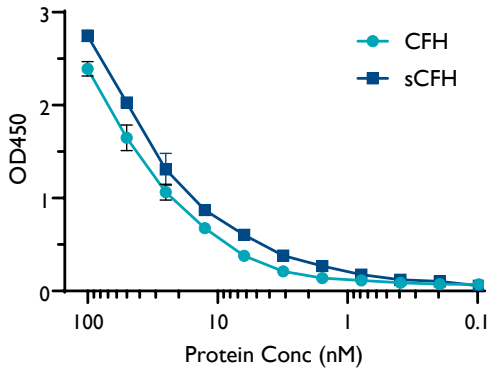
- Reduced size of the sCFH protein predicted to result in increased penetration of the RPE and choroid[2,3]

Pharmacological Activity

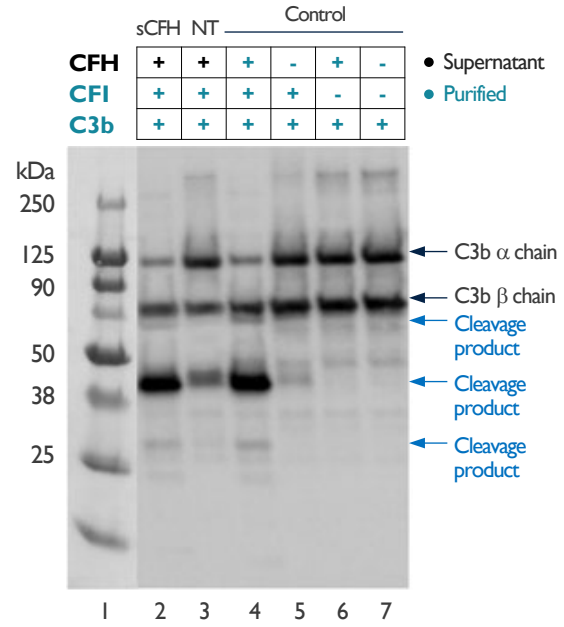
Heparin Binding



hC3b Binding



C3b Cleavage



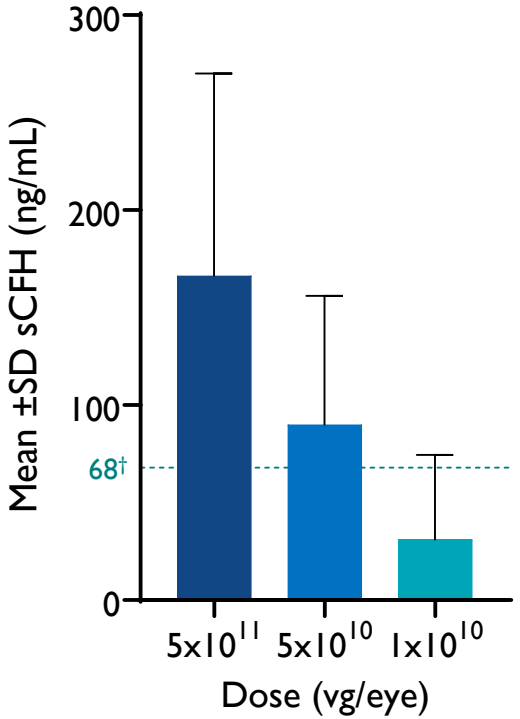
sCFH exhibits proper heparin and C3b binding and **inhibits complement activity *in vitro***

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.

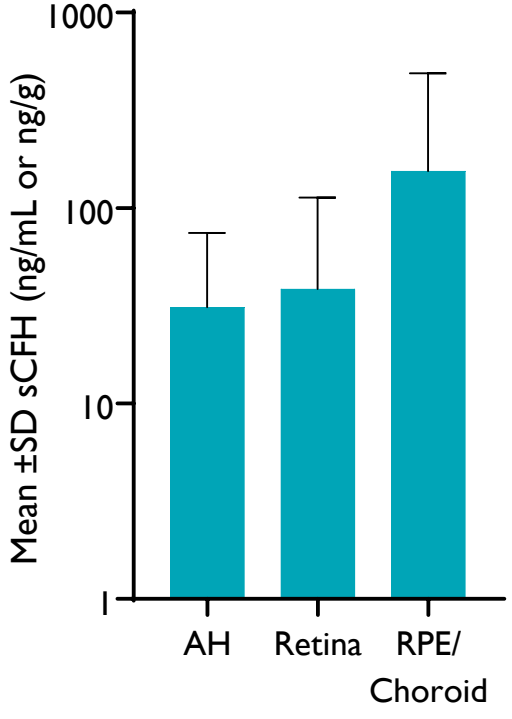
Target sCFH Concentration Levels Reached in Non-Human Primate Ocular Pharmacodynamics and Tolerability Study

4D-175 sCFH Ocular Biodistribution

Aqueous Humor*



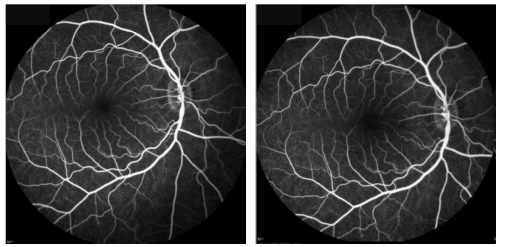
Ocular Distribution‡



4D-175 Safety and Tolerability

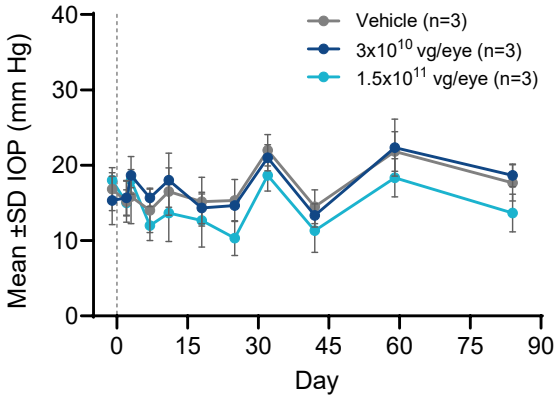
Fluorescein Angiography

NHP 2502 (1.5x10^11 vg/eye)



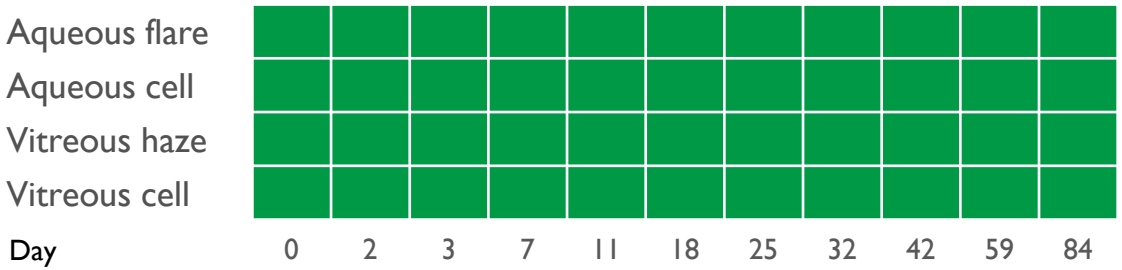
Baseline Week 12

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 Indications with the R100 Platform

VECTOR DELIVERY	PRODUCT CANDIDATE	INDICATION	EPIDEMIOLOGY (PREVALENCE)	PHASE 1	PHASE 2	PHASE 3	MILESTONES
LARGE MARKET OPHTHALMOLOGY **R100** **Intravitreal** 	**4D-150** Aflibercept + VEGF-C RNAi	**Wet AMD**	*~3M U.S./EUMM*	4FRONT-1 4FRONT-2 PRISM			✓ Phase 2a 24-week Update (N=51) ✓ Phase 2b 24-week Update (N=45) ✓ **4D-150 Wet AMD Development Day** ✓ Interim Longest Available Data Phase 1/2a, 2b ✓ Final 4FRONT Phase 3 Design ▪ **Feb 25** Phase 2b 52-week interim data ▪ **Q1:25** Initiate Phase 3 4FRONT-1 clinical trial
		Diabetic Macular Edema	*~5M U.S./EUMM*	SPECTRA			▪ **Early Jan 25** Program update
	4D-175 Short Form Complement Factor H	**Geographic Atrophy**	*~2.5M U.S./EUMM*	GAZE			✓ IND Cleared June 2024 ▪ **Q1:25** Begin Phase 1 enrollment

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

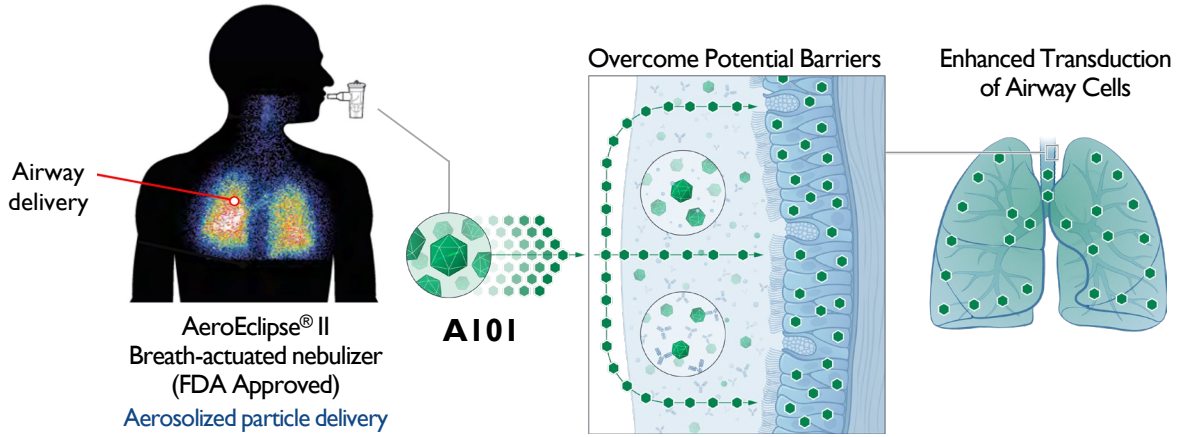
Prior aerosol gene therapy trials failed to achieve transgene expression in lung[1,2]; potential limitations:

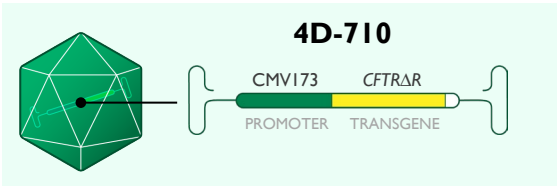
- ✕ Poor mucus penetration
- ✕ Inefficient airway cell transduction
- ✕ Suboptimal tissue tropism
- ✕ Susceptibility to clearance by human AAV immunity

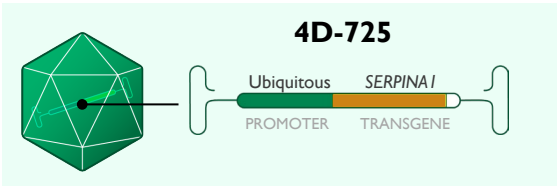
A101 invented at 4DMT to overcome these limitations:

- ✓ 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







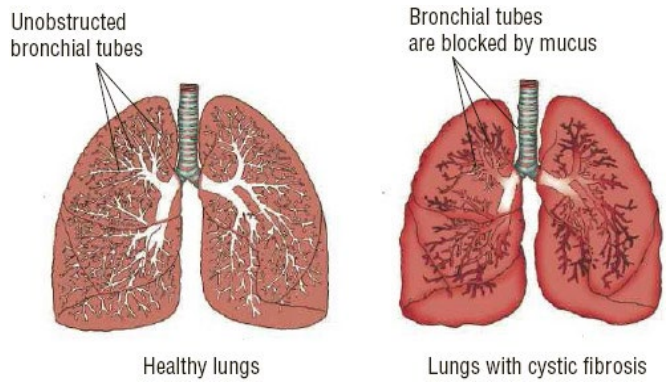
Product	Indication	Prevalence	Preclinical	Phase 1/2	Phase 3
4D-710	CF Lung Disease (mod. inelig/intol.)	*~15K WW*			
	CF Lung Disease (on modulators)	*~90K WW*			
4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EU*			

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

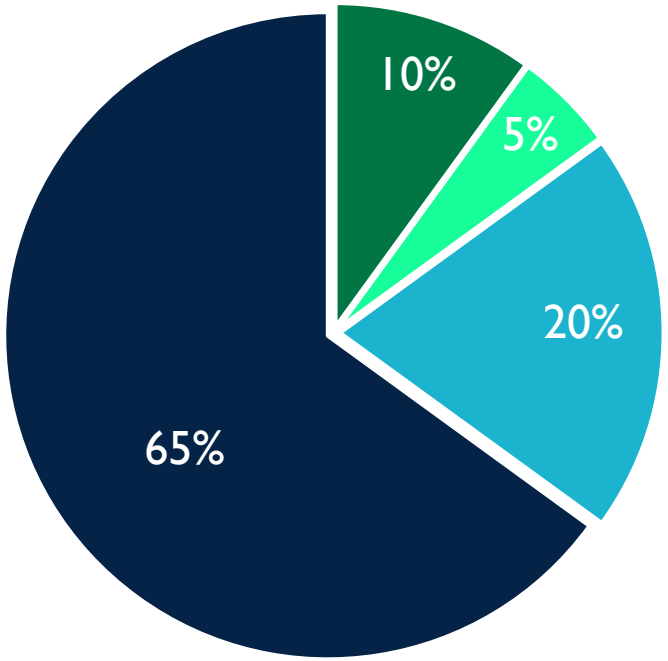
Standard of Care

- **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

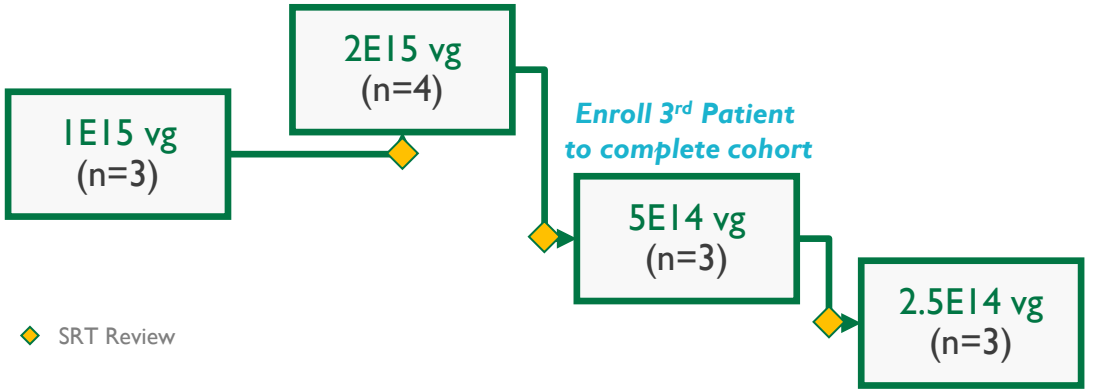
CFTR, cystic fibrosis transmembrane conductance regulator. 1. Based on assumptions derived from Middleton, 2019 and CFF registry analysis.

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

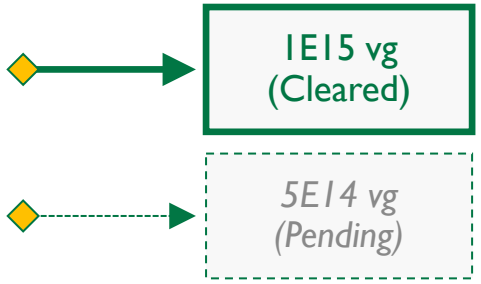
Phase 1 (Dose Exploration)

$ppFEV_1$ Eligibility Criteria: 50% to 100%



Phase 2 (Dose Expansion)

$ppFEV_1$ Eligibility Criteria:
50% to 90%



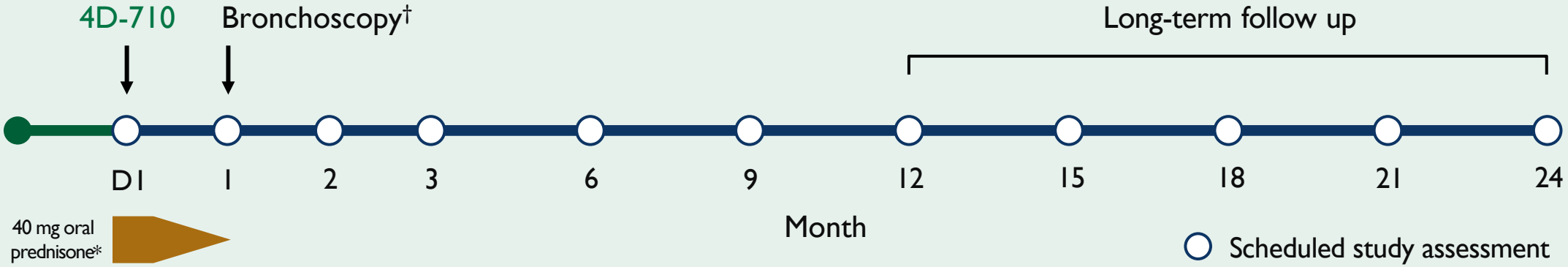
Expect to begin dosing (n= up to 9) H2 2024

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.

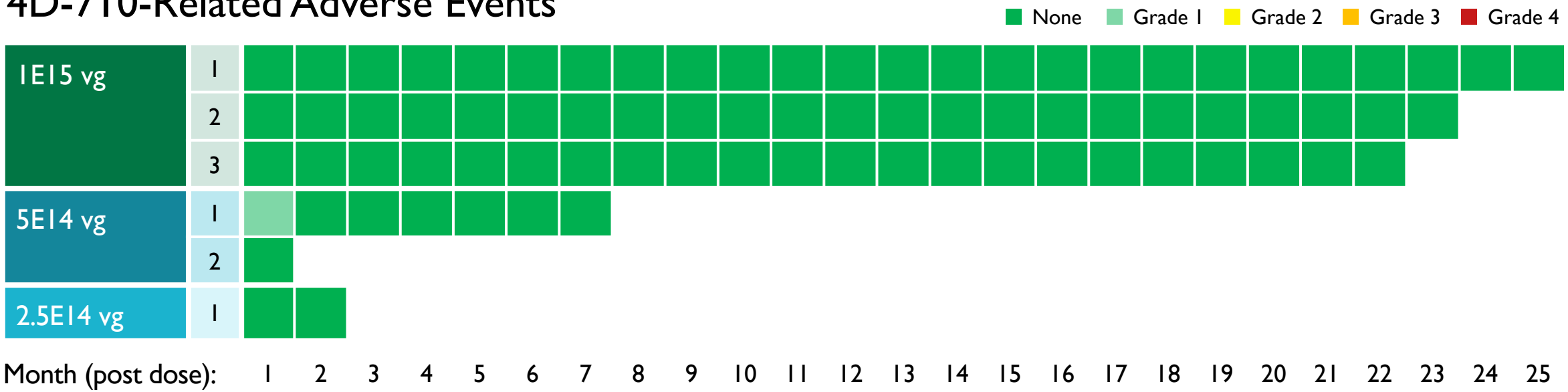
AEROW To-Date Enrolled pwCF Ineligible or Intolerant to Modulators with a Broad Range of Disease Activity, 5 with Pre-Existing Immunity to A101

	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

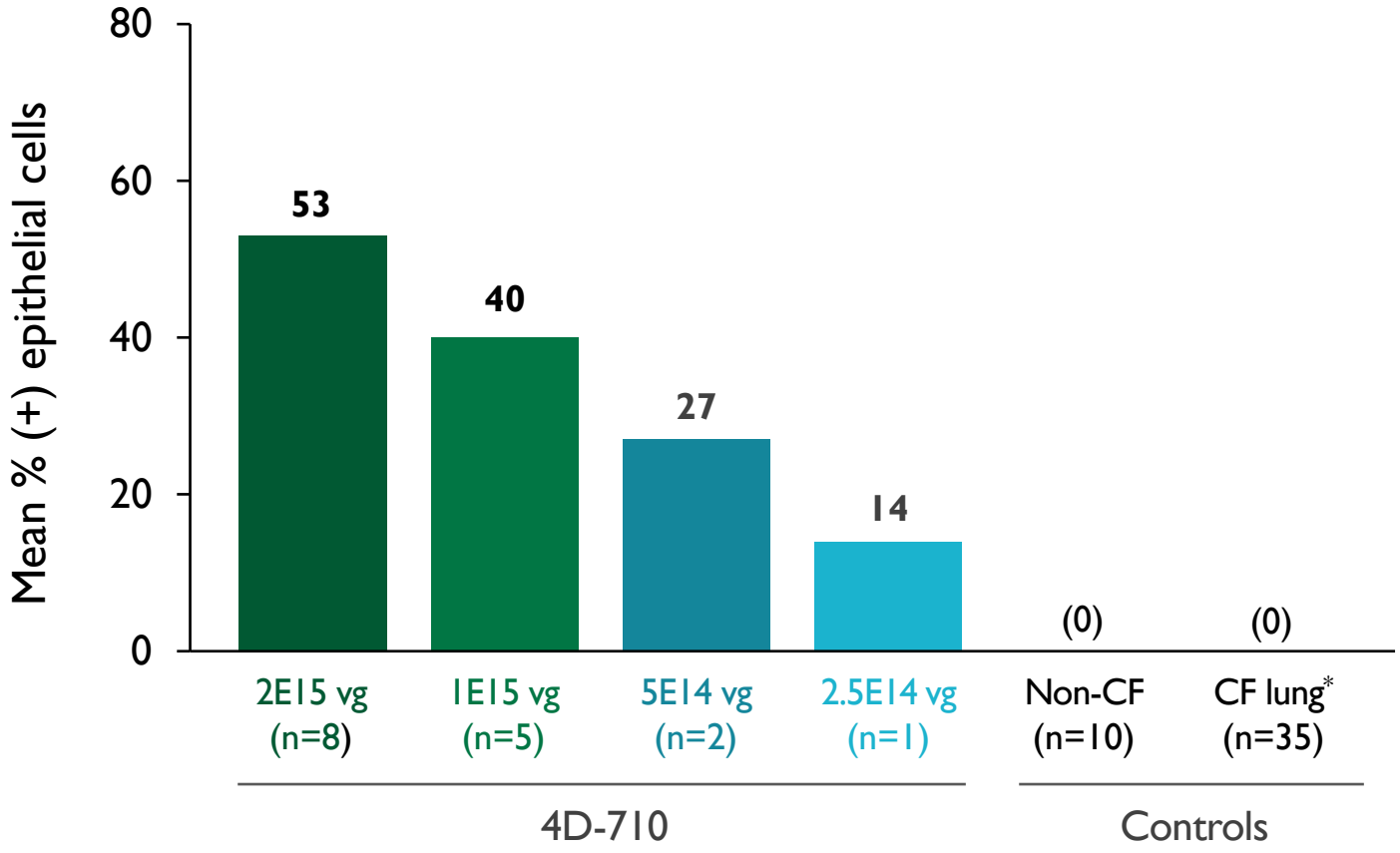


- Administration of aerosolized 4D-710 well tolerated
  - No dose-limiting toxicities
  - No 4D-710–related SAEs
  - No clinically significant 4D-710-related adverse events after administration
- No inflammation or toxicity in lung biopsies samples

Best available data as of May 24, 2024.

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

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

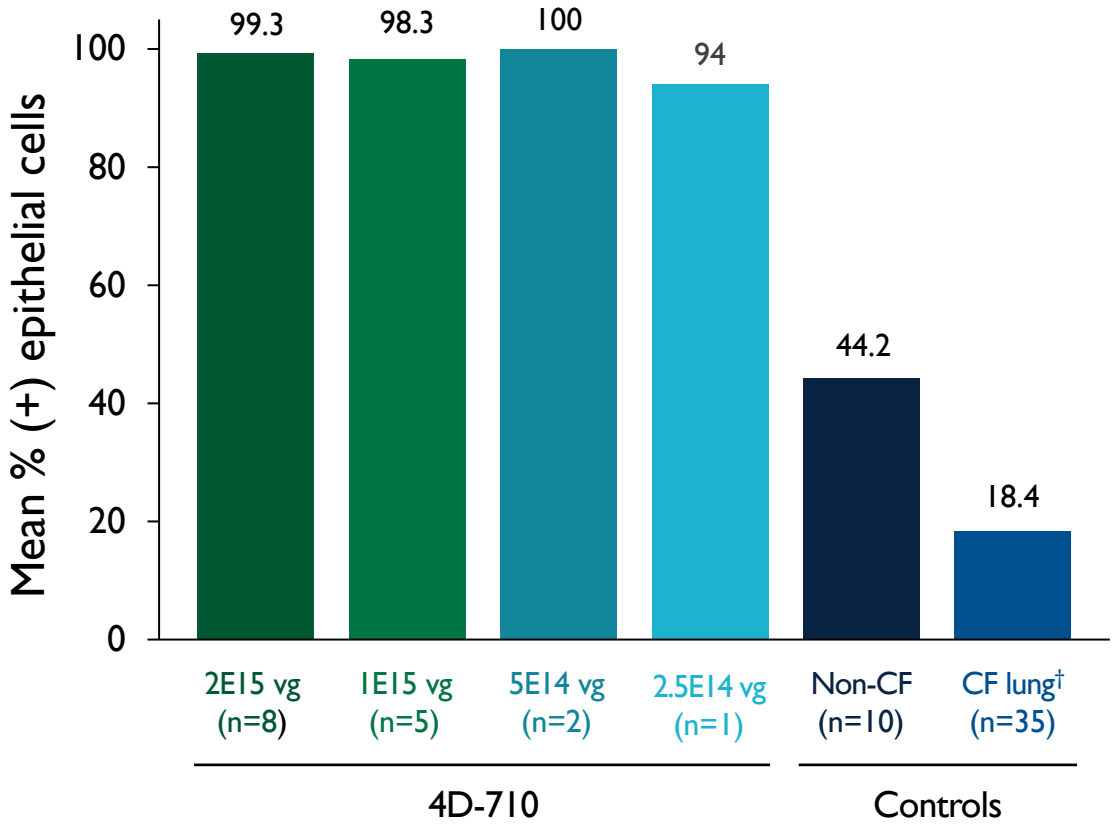


- Dose-dependent *CFTRΔR* mRNA expression in bronchial epithelial cells
- No *CFTRΔR* mRNA expression observed in commercial non-CF and CF lung samples
- Commercial non-CF samples positive for endogenous *CFTR* mRNA expression

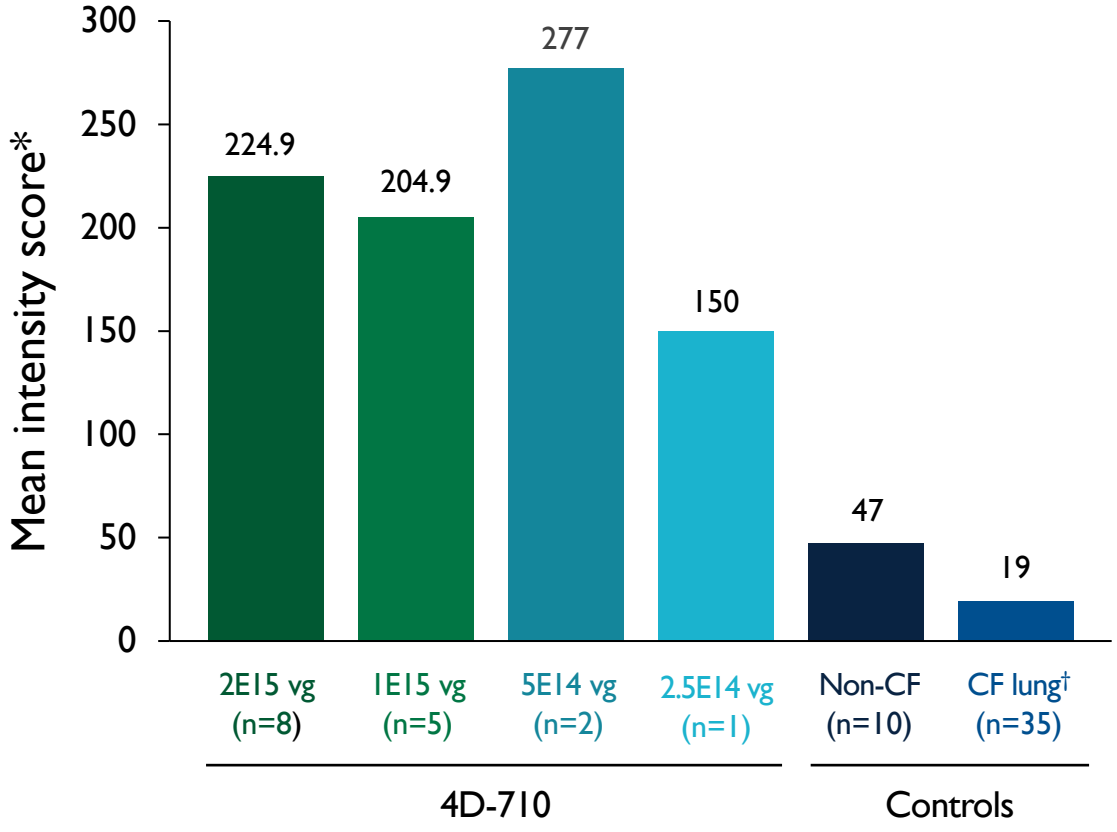
Best available data as of May 24, 2024. Quantification by Visiopharm® AI Machine Learning Analysis. Number shown below each group indicates the number of lung samples. *Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were ΔF508 homozygous mutations.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



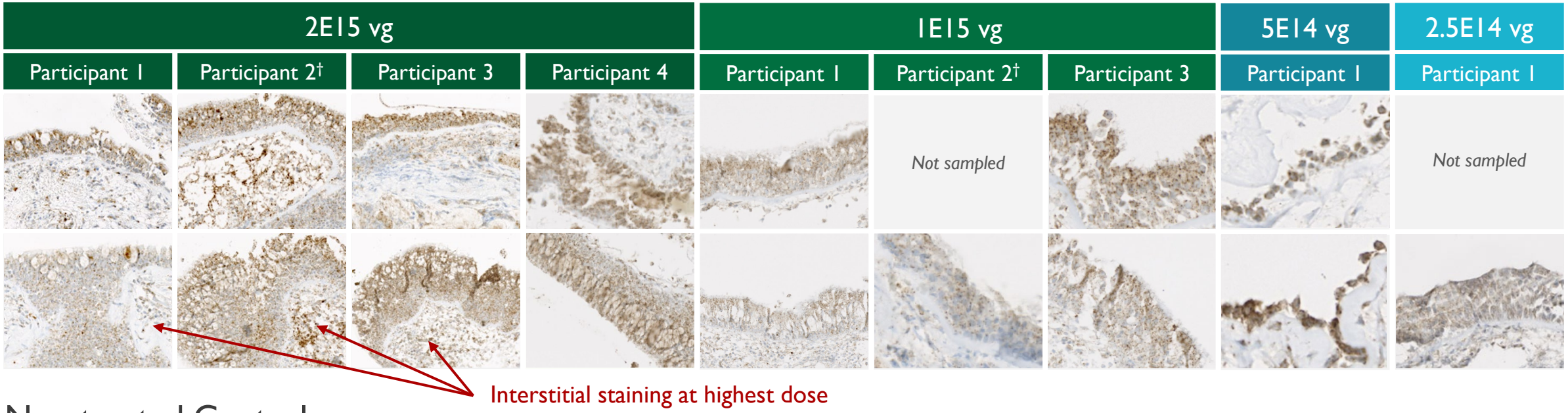
CFTR Staining Intensity (IHC)*



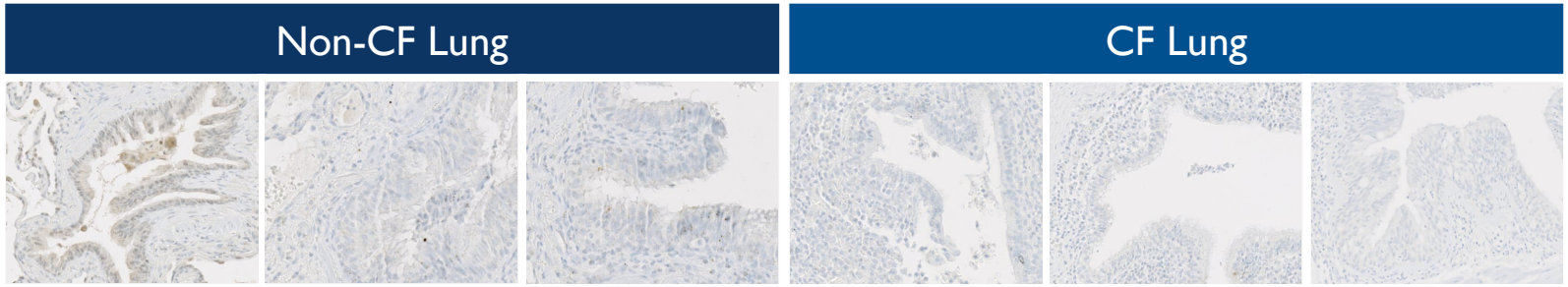
Best available data as of May 24, 2024. Quantification by Visiopharm AI Machine Learning Analysis. Number shown below each group indicates the number of lung samples. *H-score. †Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were ΔF508 homozygous mutations.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

Widespread & Consistent CFTR Protein Expression: 100% of Samples

4D-710 Treated



Non-treated Controls

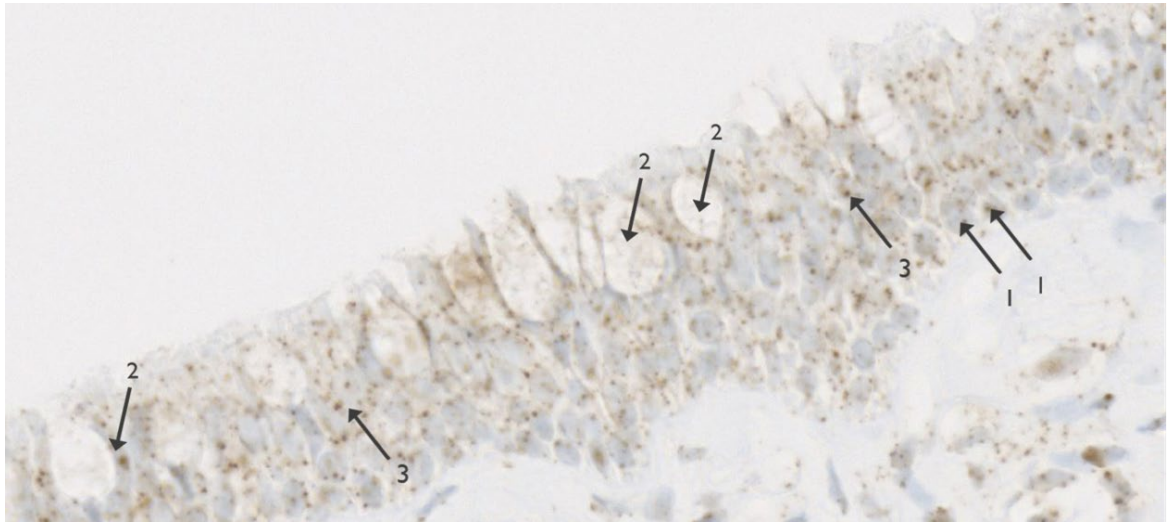


Best available data as of May 24, 2024. *Representative images, endobronchial biopsy samples obtained from the left secondary carina (row 1) and right middle lobe (row 2). †Endobronchial biopsy performed at Week 8.

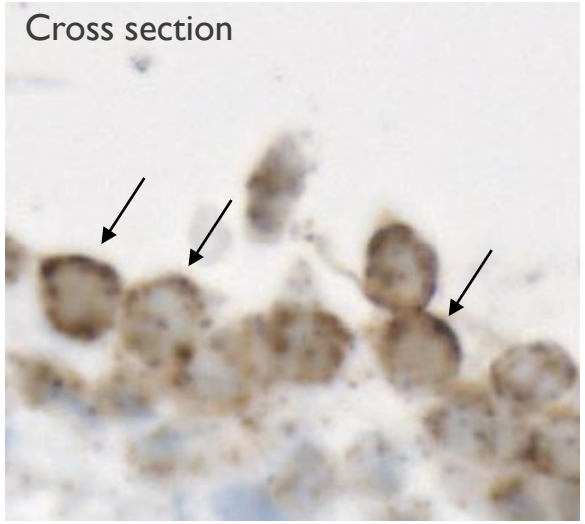
CFTR Protein Expression Observed in Multiple Airway Cell Types

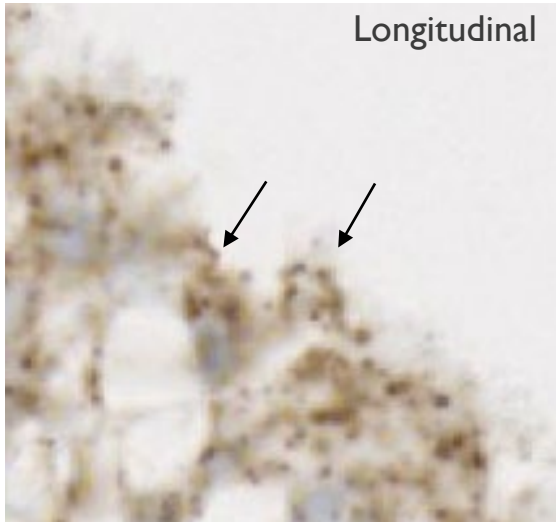
CFTR Protein Expression (IHC) Following Administration of 4D-710: Secretory, Ciliated & Basal Cells

CFTR Protein Expressed in Multiple Cell Types*



Localization to Apical Region†

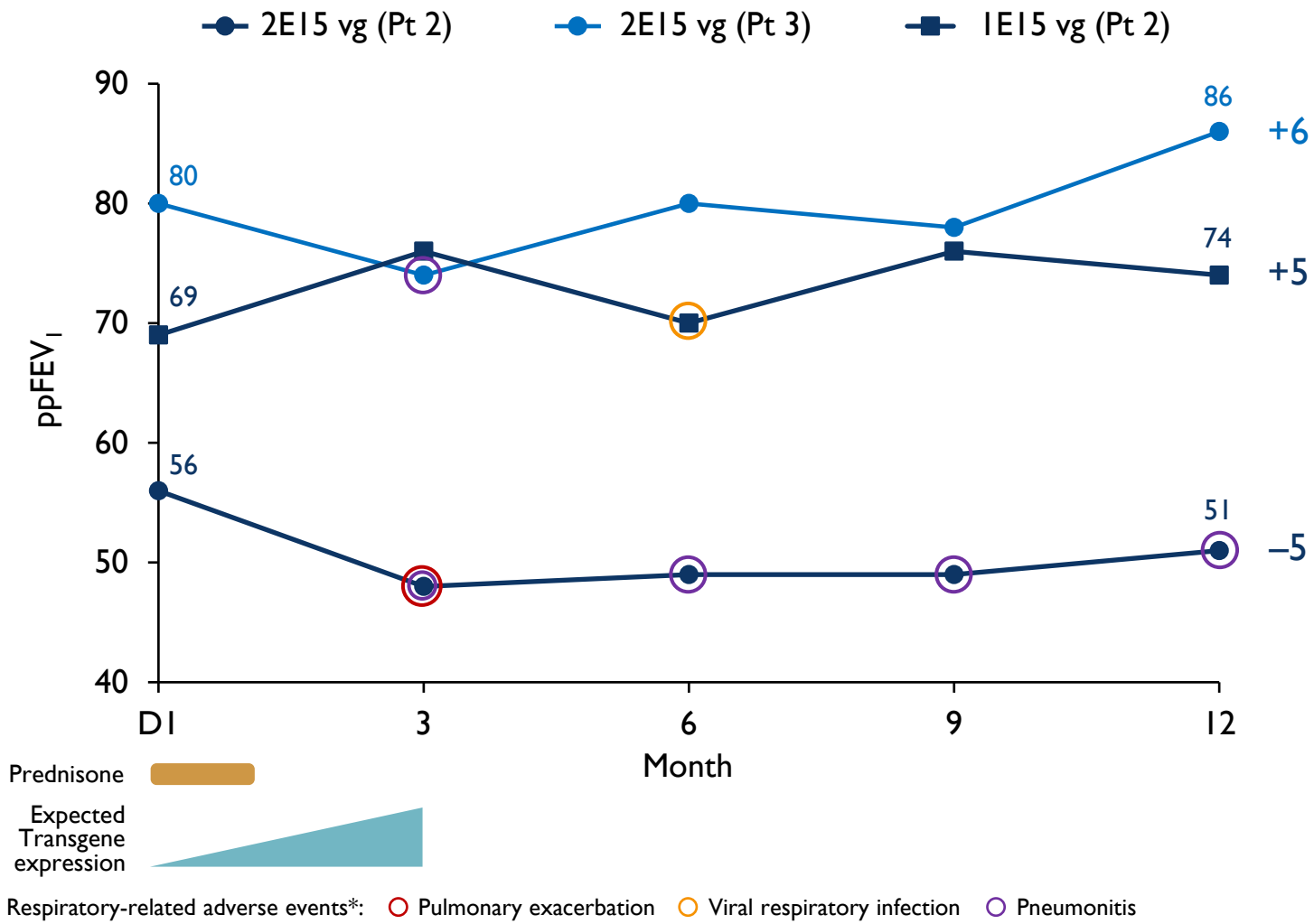




(**1**) Basal cells (**2**) Goblet cells (**3**) Columnar ciliated cells

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.

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

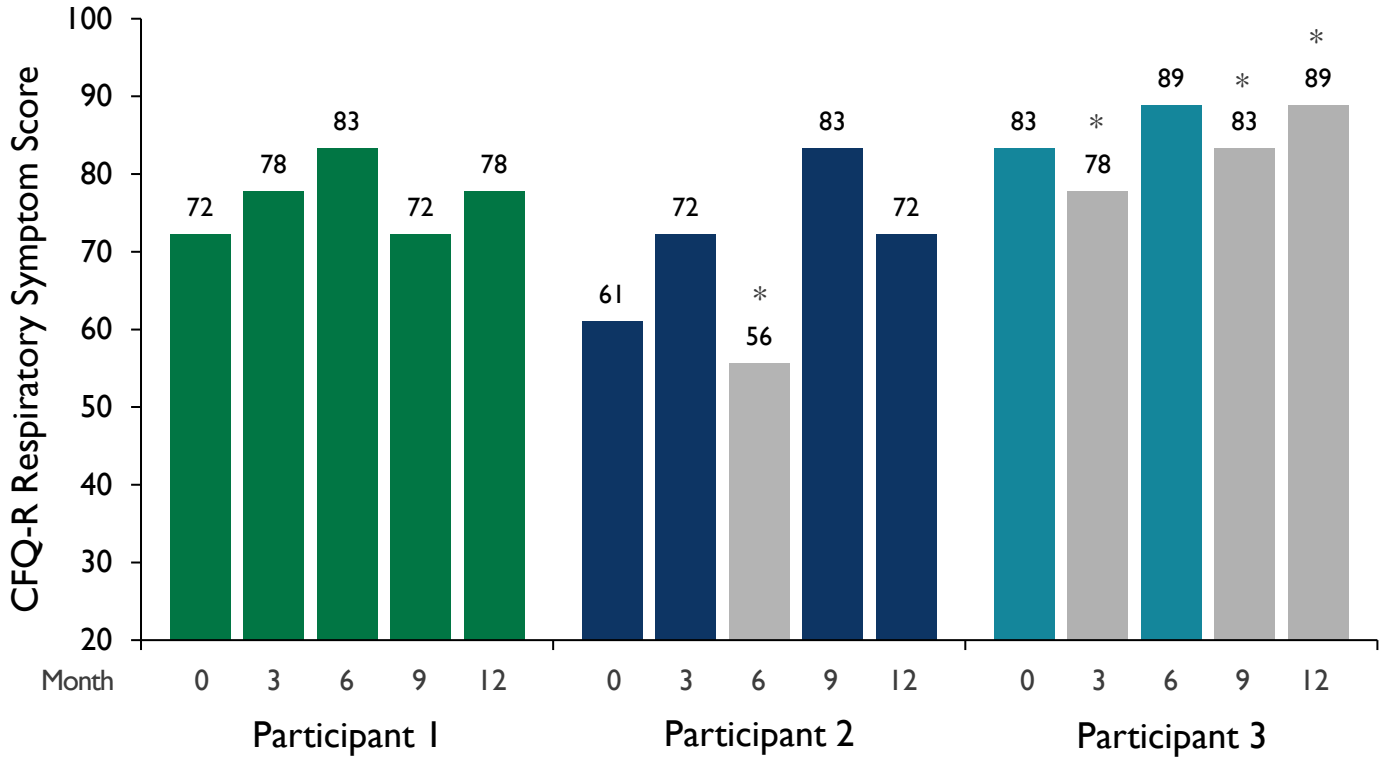


- Three participants had a baseline ppFEV$_1$ ≤80% and >6 months of follow up
- Two showed improvement in ppFEV$_1$ at 12 months
  - 2E15 vg (n=1): +6%
  - 1E15 vg (n=1): +5%

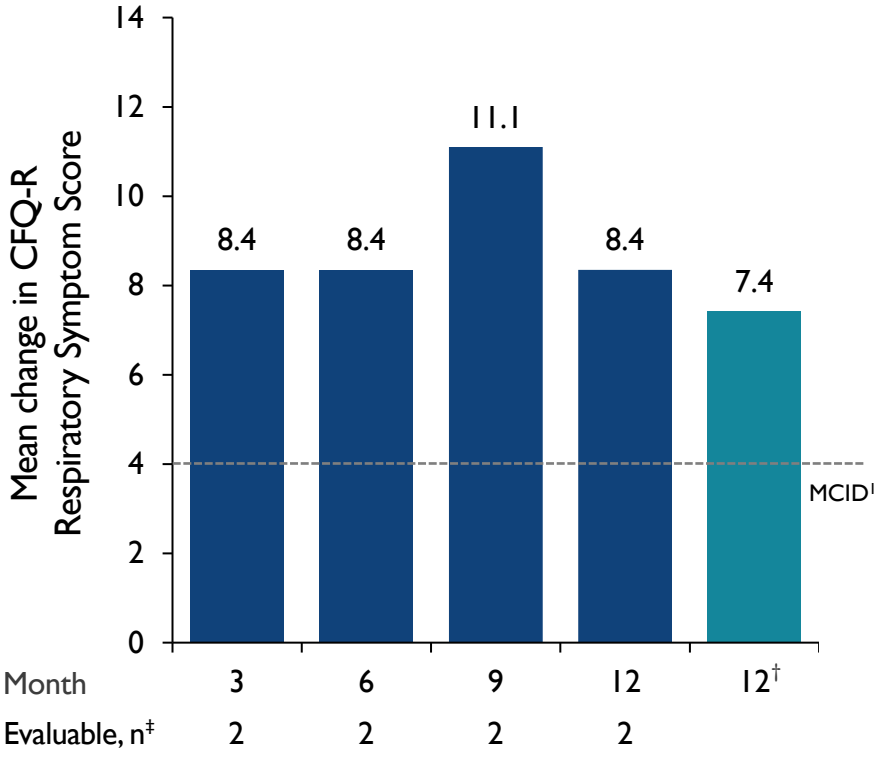
Best available data as of May 24, 2024.

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.

Pulmonology Pipeline Key Expected Milestones

VECTOR DELIVERY	PRODUCT CANDIDATE	INDICATION	EPIDEMIOLOGY (PREVALENCE)	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			✓ Phase 1 interim update (N=10) ▪ **Mid-2025** Interim data & program update
		Cystic Fibrosis Lung Disease (on-modulators)	*~90K WW*	AEROW			▪ **Mid-2025** Program update
	4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EUMM*				▪ **Early Jan 25** Program update

4DMT

CARDIOLOGY

Vector: C102

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

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

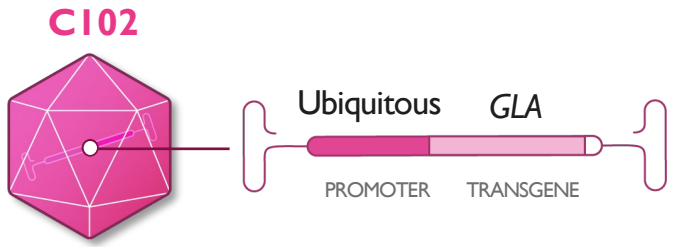
Cardiac disease is the most common cause of death (75%)[1] in Fabry disease

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

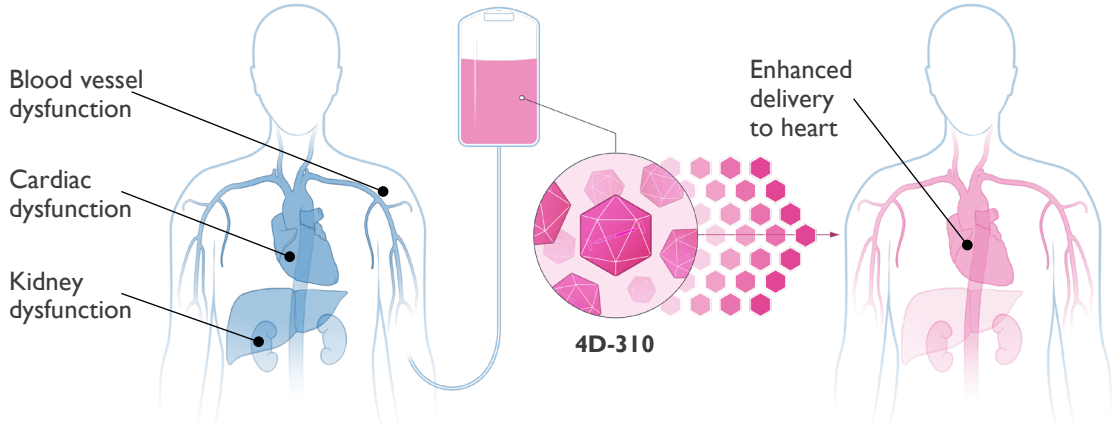
4D-310



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

Transgene: *GLA* (encodes AGA enzyme)

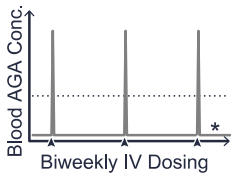
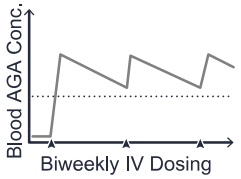
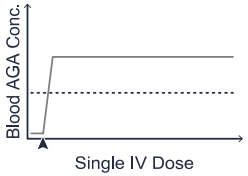
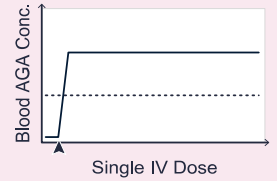
Promoter: Ubiquitous



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.

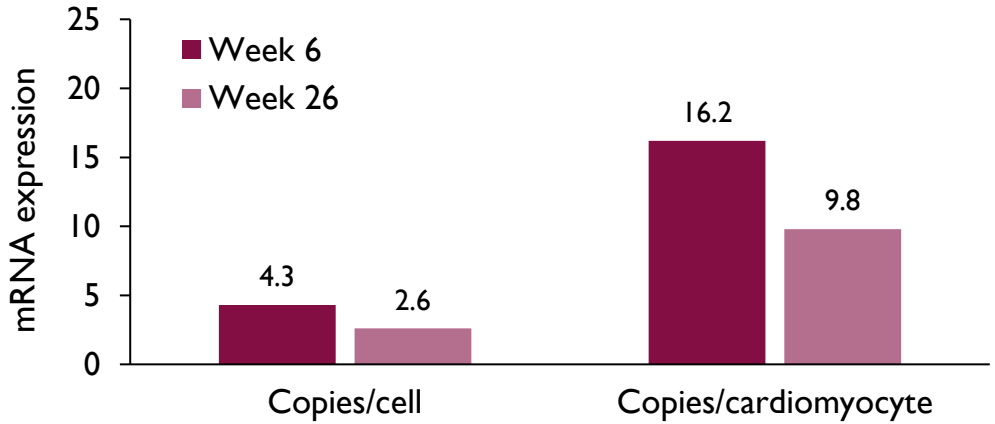
Baseline Patient Characteristics

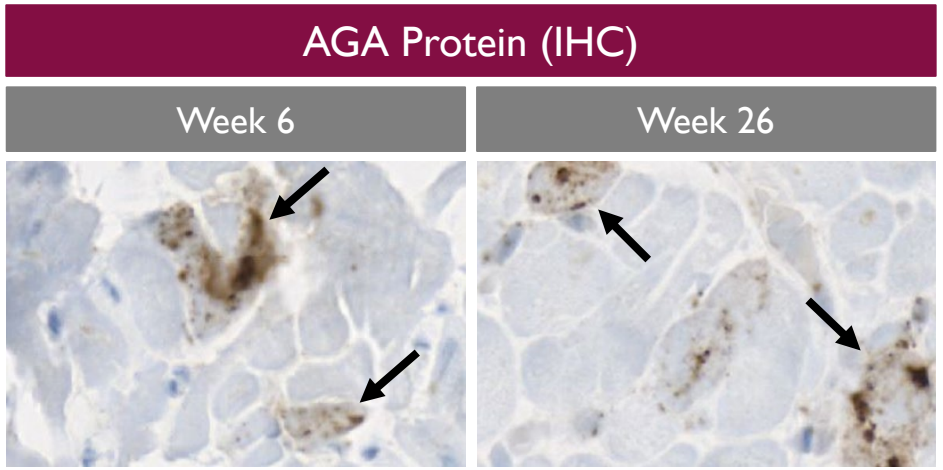
	INGLAXA 1				INGLAXA 2	
Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Disease classification	Classic	Classic	Classic	Late onset	Late onset	Late onset
GLA variant	c.1023A>C	c.708G>T	c.974G>A	c.671A>G	IVS4+919 G>A	c.644 A>G
Serum AGA activity, nmol/hr/mL*	0.42	0.00	0.30	0.06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

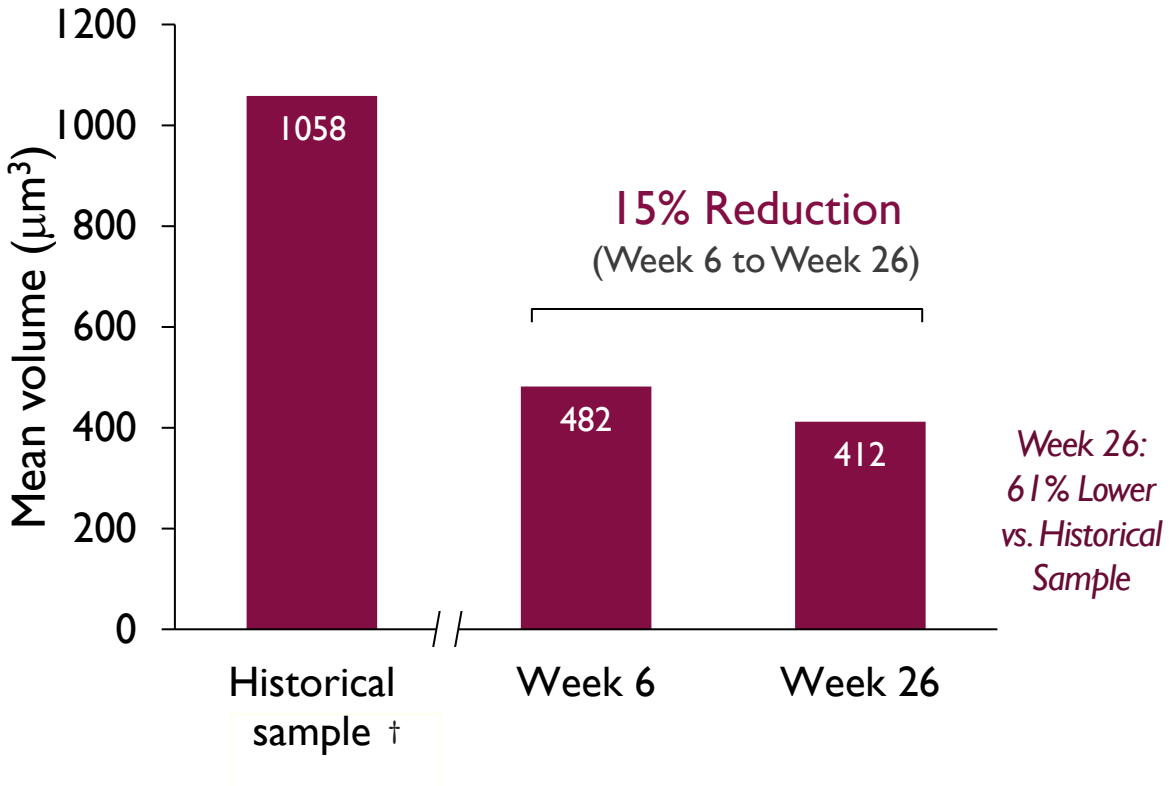




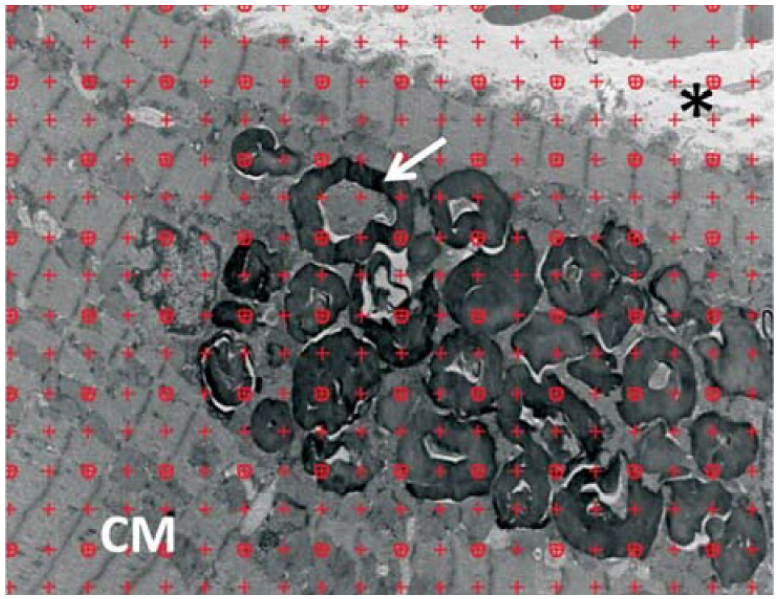
*Male (57 y) with late-onset Fabry disease. †Calculated based on an estimated 30% ratio of cardiomyocytes to total heart cells. IHC, immunohistochemistry; ISH, *in situ* hybridization; qPCR, quantitative polymerase chain reaction; RT-qPCR, reverse transcription-qPCR.

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**

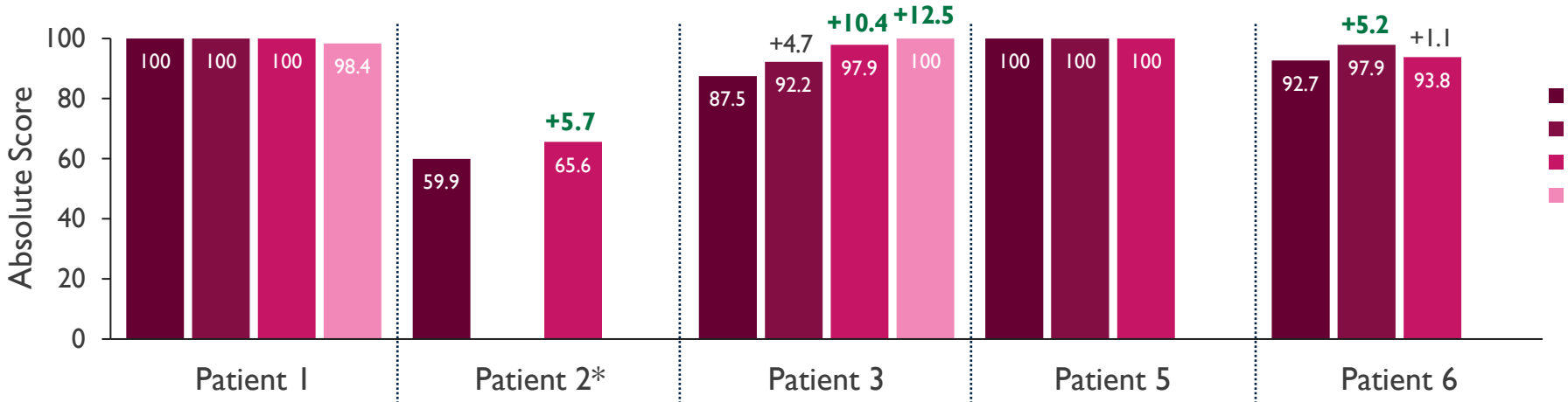
MCID=
1.5 mL/kg/min[1]

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.

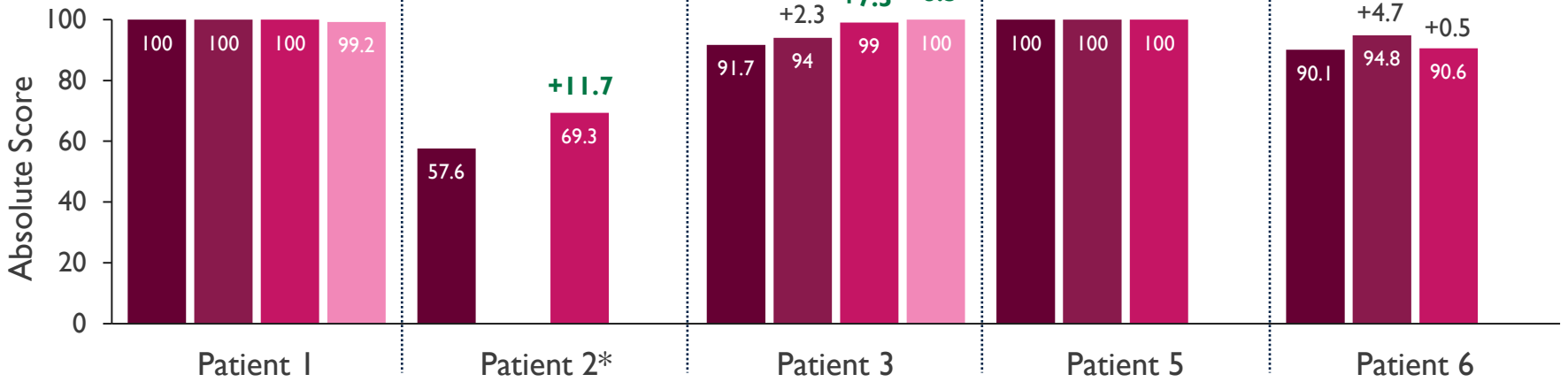
Kansas City Cardiomyopathy Questionnaire (KCCQ): Improved or Stable QoL in All Evaluable Participants

Clinical Summary Score



MCID= 5 points[1]

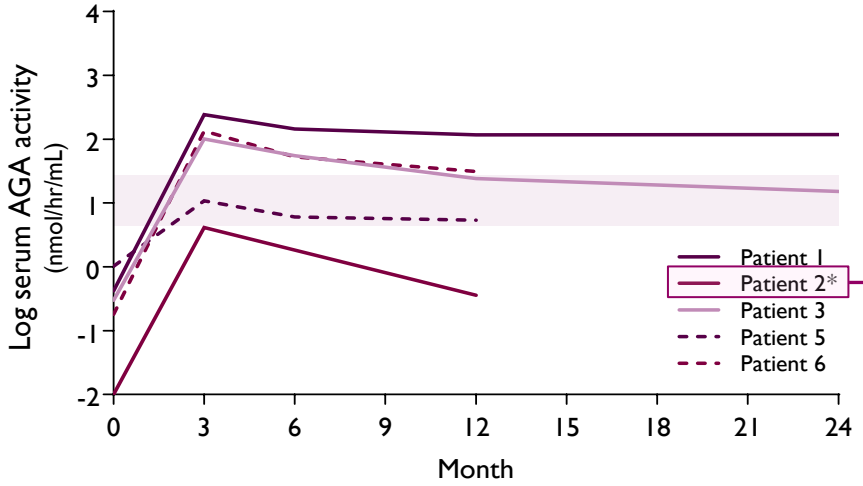
Overall Summary Score



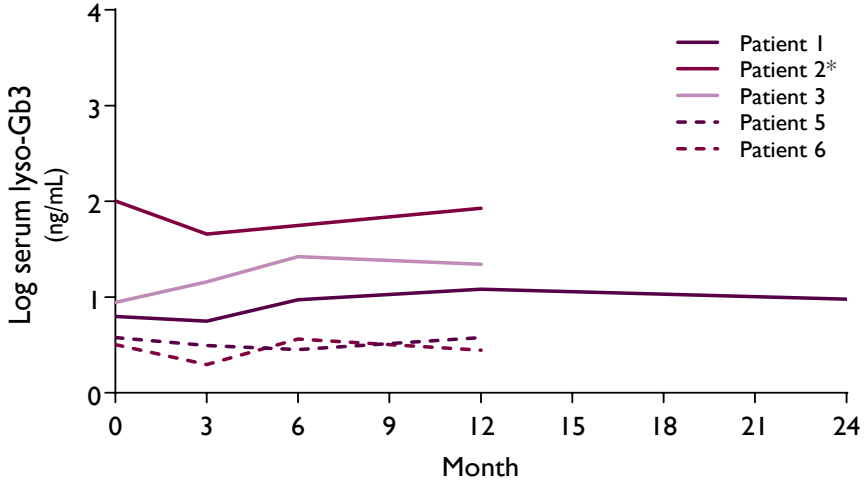
Scores range from 0 to 100 (higher score=less severe); minimal clinically important difference (overall summary score), 5 points [1]. *High antibody titer; entered study off ERT. 1. Spertus JA et al. JACC 2020;76:2379–90.

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.

Program Expectations & Cash Position

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

Large Market Ophthalmology	4D-150 **Wet AMD**	✓ 24-week landmark from Phase 2a Dose Expansion (N=51) at Angiogenesis: **February 3, 2024**
		✓ 24-week landmark Phase 2b Population Extension (N=45) at ASRS: **July 17, 2024**
		✓ **4D-150 Wet AMD Development Day: September 18, 2024** ✓ Interim longest available follow up data through up to 2.5 years from PRISM Ph1/2a, 2b cohorts ✓ Final 4FRONT Phase 3 clinical trial design update
		52-week landmark from Phase 2b Population Extension: **February 2025**
		Initiation of Phase 3 4FRONT-1 clinical trial: **Q1 2025**
	4D-150 **DME**	SPECTRA clinical trial program update: **Early January 2025**
	4D-175 **GA**	✓ IND filing: **Q2 2024** Begin enrollment of Phase 1 GAZE clinical trial: **Q1 2025**
Pulmonology	4D-710 **CF**	Interim data & program update from AEROW clinical trial: **Mid-2025**
Cash Balance		**$551M cash as of September 30, 2024** (Unaudited); **Runway into H1 2027**

THANK YOU

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