



Genetic Medicines, Redefined

Corporate Presentation

July 2026

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REDEFINING GENETIC MEDICINES

**Durable & disease-targeted therapeutics
for large market diseases**

Lead Product: 4D-150

Next Generation, Locally Delivered AAV Genetic Medicines Pipeline: Focused on Rapidly Advancing 4D-I50 to Global Commercialization

Therapeutic Area Vector	Product Candidate	Indication	Pre-clinical	Phase I	Phase 2	Pivotal	BLA Filing	Partners
RETINA R100  Intravitreal	4D-I50	Wet AMD						 Otsuka APAC Rights 4DMT: U.S./EU/ROW
		DME						
	4D-I75	Geographic Atrophy						Open IND, evaluating strategic funding alternatives
PULMONOLOGY A101  Aerosol	4D-710	CF lung disease						 CYSTIC FIBROSIS FOUNDATION Fully Funded
	4D-725	AIAT lung disease						CIRM CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE Fully Funded through IND

4DMT's Innovation is Redefining Genetic Medicines to Empower Broad Commercial Adoption

Characteristics:	Conventional Genetic Medicine Barriers	4DMT Medicines Target Profile
Diseases(s) Targeted	 Rare diseases	 Large market diseases: sustainable commercial markets
Route of Delivery & Safety Risk	 Complex (surgical, systemic), with challenging safety management	 Simple delivery and best-in-class safety
Pivotal Trial	 Negotiated & non-standard regulatory pathways	 Global regulatory alignment
Manufacturing	 High COGS	 Low COGS
Commercial Potential	 High prices, payer barriers & limited global potential	 Low prices, fewer payer barriers & broad global potential



4D-150 

Potential Backbone Therapy for Treatment of Retinal Vascular Diseases

Wet Age-related Macular Degeneration (Wet AMD)

Diabetic Macular Edema (DME)



4D-I 50

GOAL: To transform the standard of care for large market retinal vascular diseases with a safe, in-office & durable lifelong backbone therapy

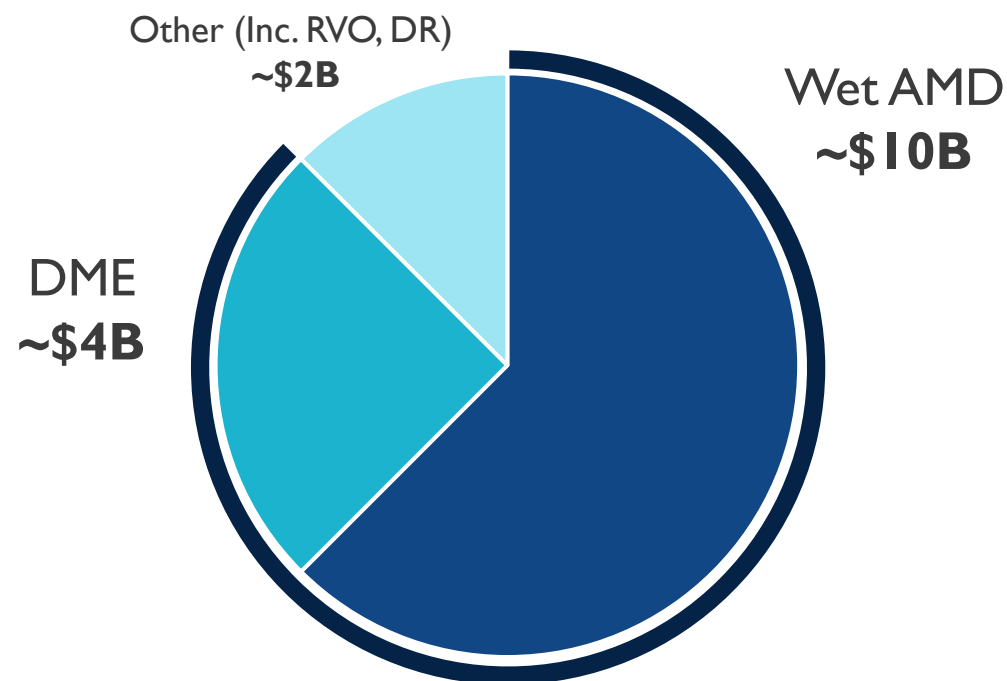
1. **Continuous disease control** enabled by **durable** retinal expression of **aflibercept**
2. **Global Phase 3 program** for Wet AMD & DME
3. **Paradigm-shifting durability** from incremental interval extension to potential **lifelong disease control & vision preservation**

4D-150 Potential to be Highly Disruptive in a Rapidly Growing, \$14B+ Market

Prevalence (2025E)

- **Wet AMD:**
 - ~5M prevalence in U.S., Europe, Japan
 - ~300K new cases diagnosed annually
- **Diabetic Macular Edema (DME):**
 - ~4M prevalence in U.S., Europe & Japan
 - ~300K new cases diagnosed annually
- Top causes of **permanent vision loss**
- **Rapidly growing population driven by aging demographics**

\$16B Global Branded Retinal Vascular Disease Anti-VEGF Market (2025E)

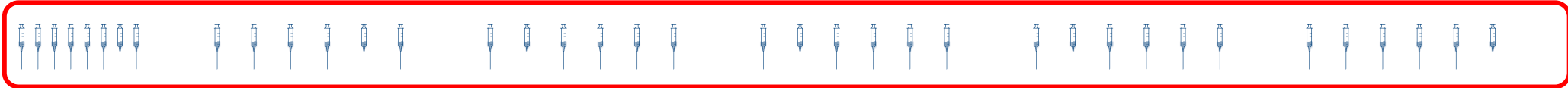


Wet AMD + DME: ~\$14B

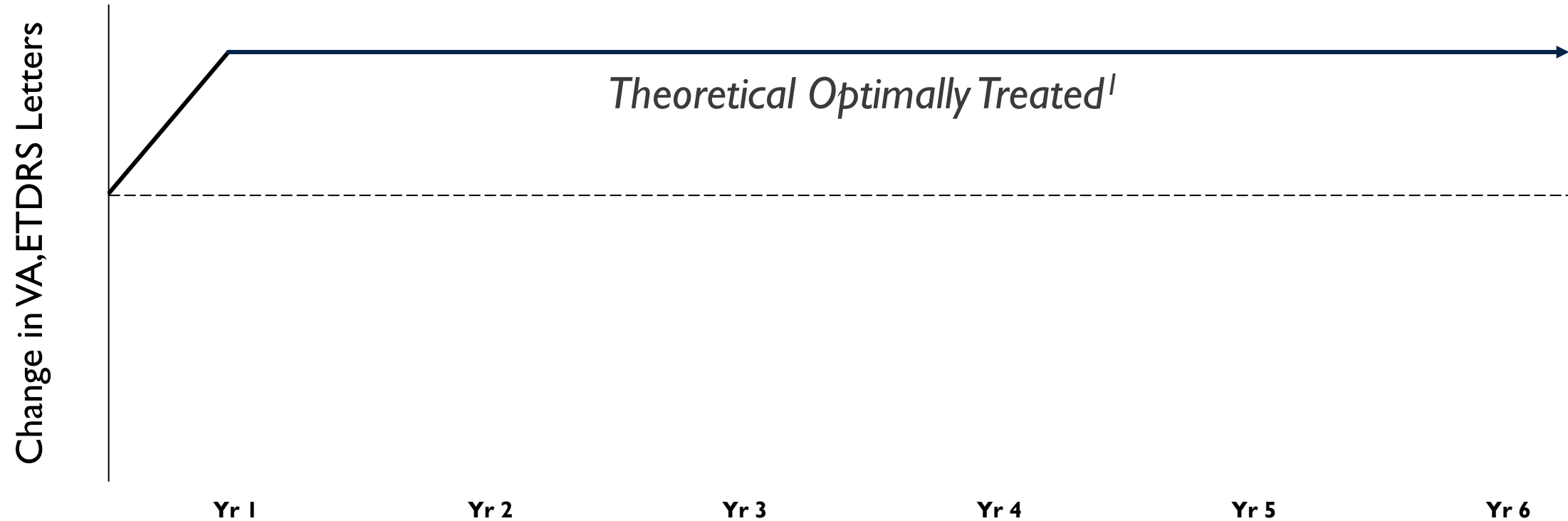
Prevalence sourced from Marketscope Retina Market Report 2023. Anti-VEGF market sourced from GlobalData, GrandView Research.

Lifelong Bolus Anti-VEGF Injections Required to Maintain Vision

LIFELONG
Bolus Anti-VEGF



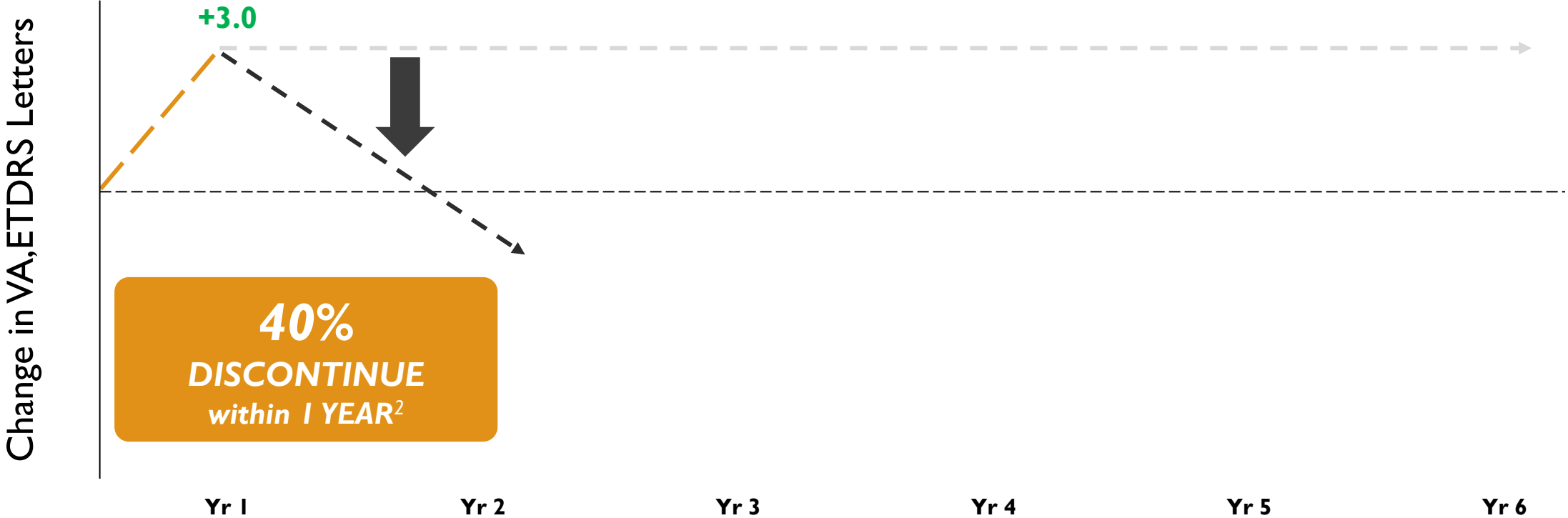
~30 Injections over 5 Years



1. Holz FG, et al. *British Journal of Ophthalmol* 2015;99:220-226. More visits and injections appeared to be correlated with more successful maintenance of visual acuity gains, including in SEVEN-UP (Seven Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials),

In the Real World, the Bolus SoC is Unsustainable... Leading to **High Discontinuation Rates**

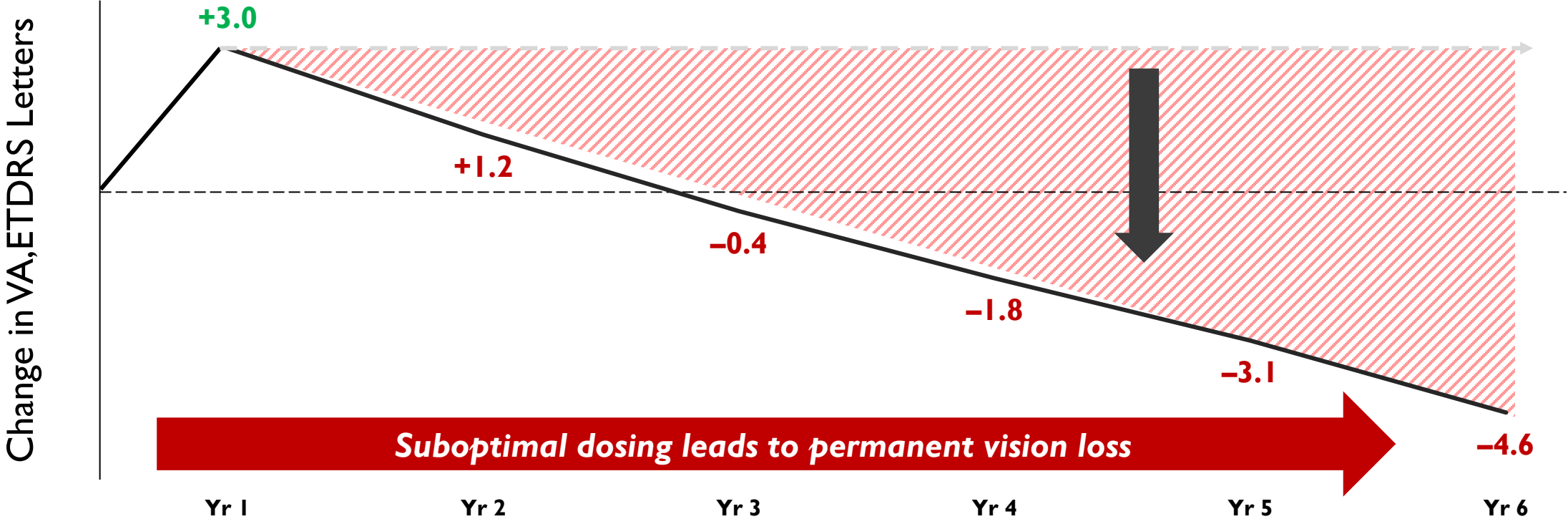
LIFELONG
Bolus Anti-VEGF



1. Wykoff et al.: *Ophthalmol Sci.* 2023 Oct 31;4(2):100421.; n=135,384 at Yr 1, 6,878 at Yr 6. 2. Khanani AM, et al. *Ophthalmol Retina.* 2020;4(2):122-133

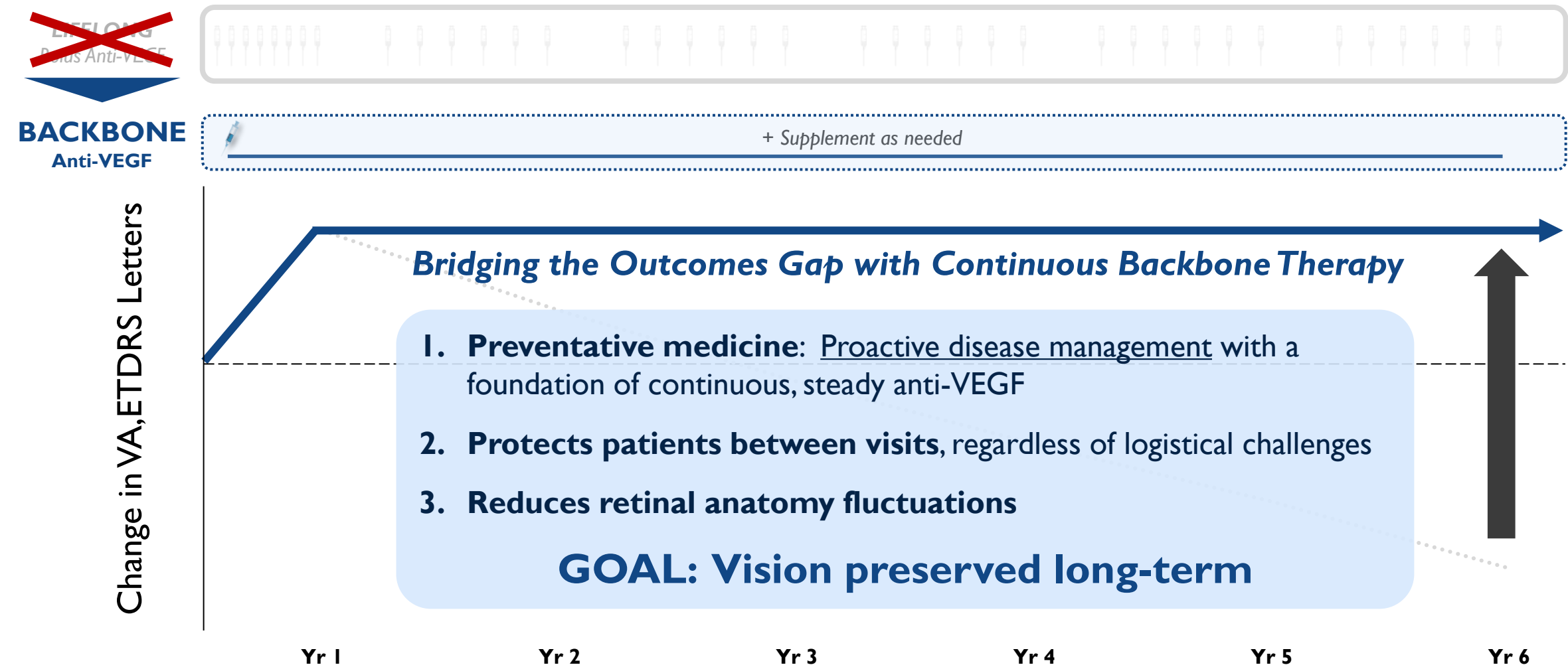
In the Real World, the Bolus SoC is Unsustainable... Leading to **Unrelenting Vision Loss**¹

LIFELONG
Bolus Anti-VEGF



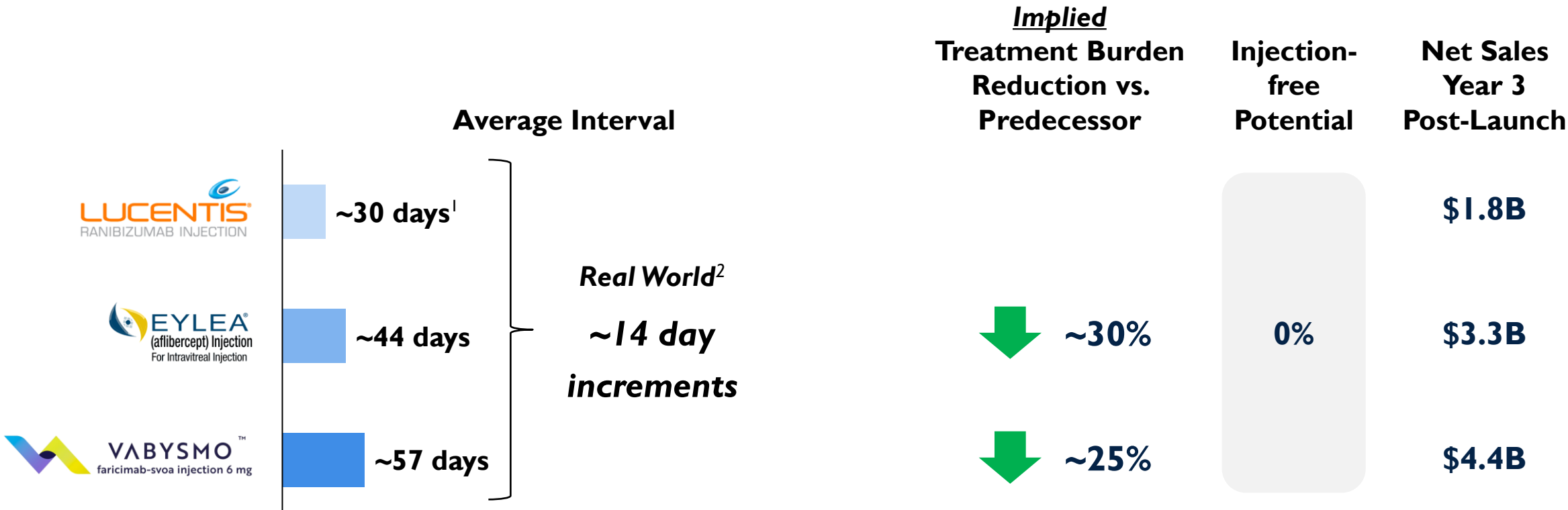
¹ Wyckoff et al.: *Ophthalmol Sci.* 2023 Oct 31;4(2):100421.; n=135,384 at Yr 1, 6,878 at Yr 6.

Solution: One-time Backbone Treatment for Continuous Disease Control & Vision Protection By Significantly Reducing Treatment Burden



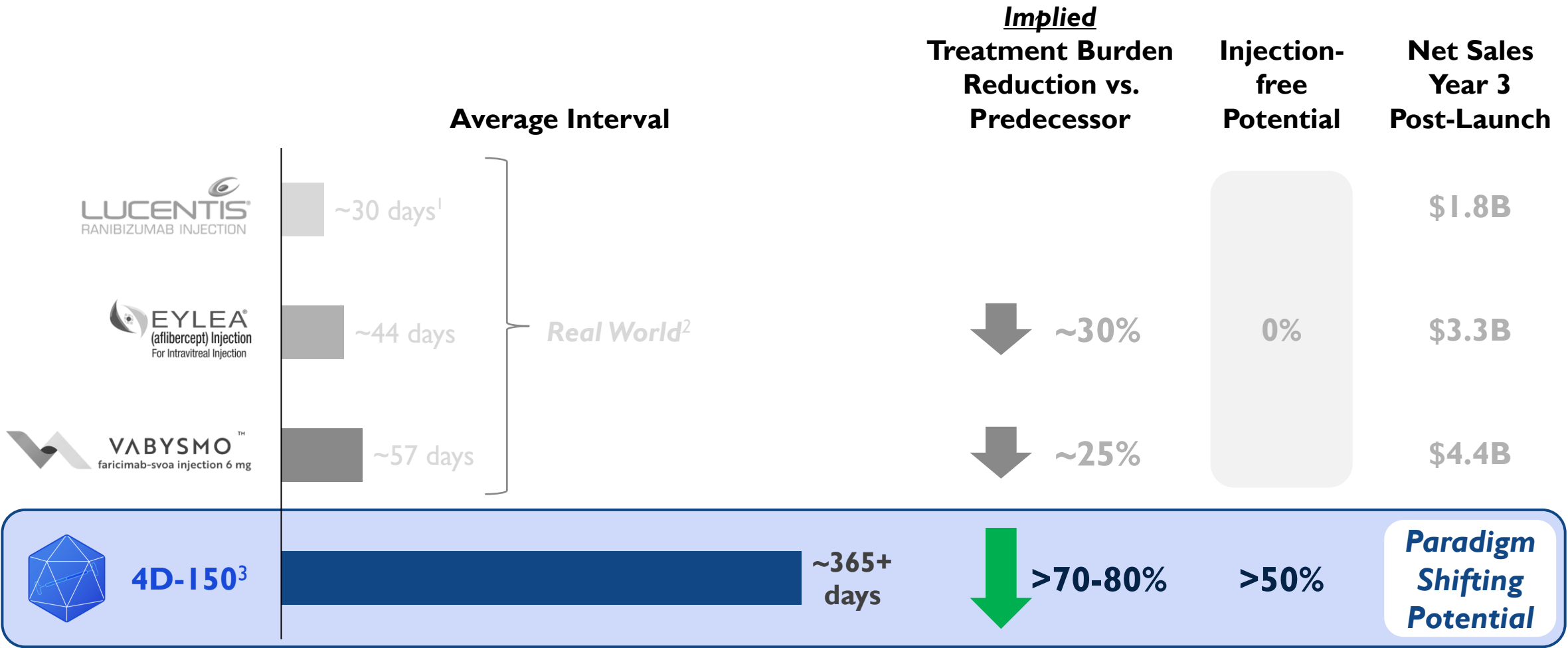
Wykoff et al.: Ophthalmol Sci. 2023 Oct 31;4(2):100421.; n=135,384 at Yr 1, 6,878 at Yr 6

Despite Incremental Durability Improvements, Eylea & Vabysmo Had Rapid, Blockbuster Commercial Success



1. Lucentis package insert; 2. Real-World Evidence (TRUCKEE Study). Injection Burden Reduction vs. prior therapy implied based on difference calculated annual injections based on TRUCKEE durability.

4D-I50 Durability Profile would be Paradigm-Shifting

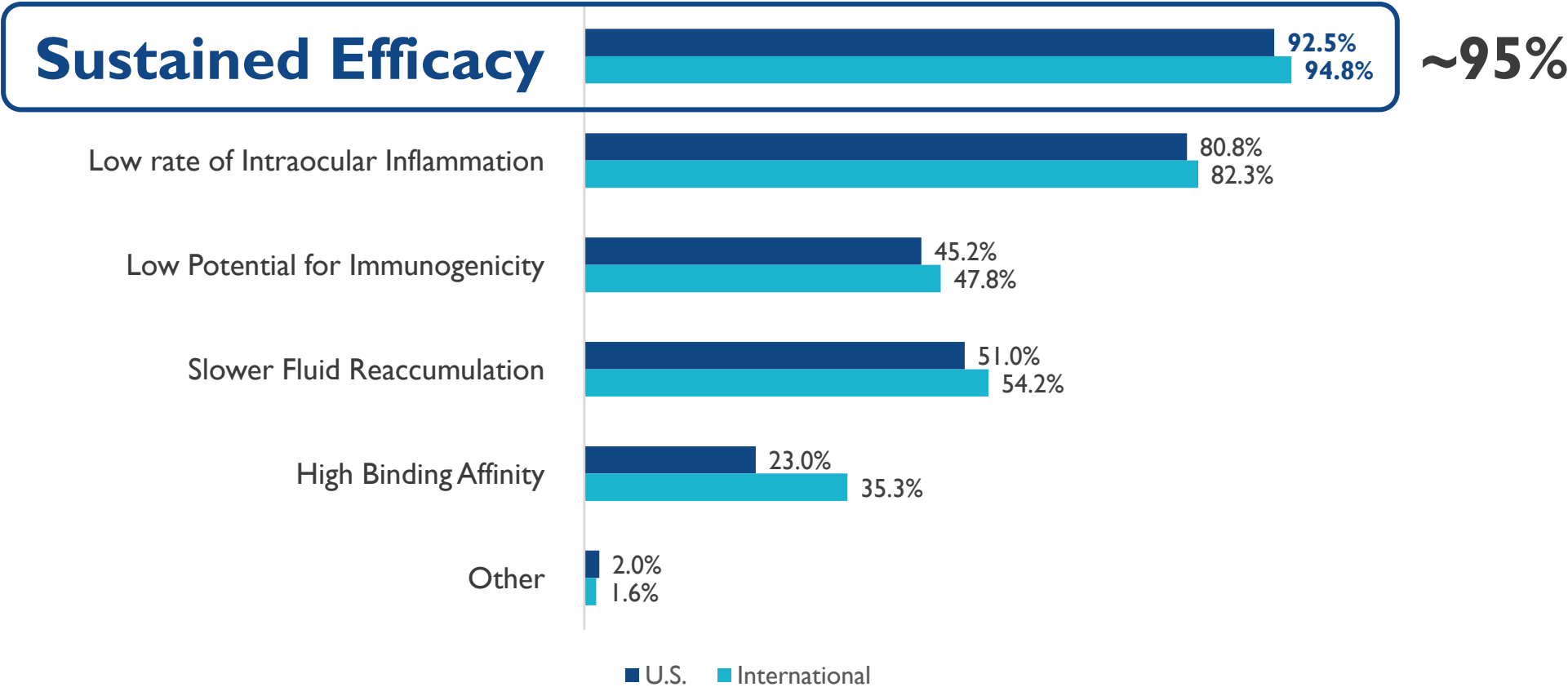


1. Lucentis package insert; 2. Real-World Evidence (TRUCKEE Study). Injection Burden Reduction vs. prior therapy implied based on difference calculated annual injections based on TRUCKEE durability. 3. 4DMT PRISM Phase 2b data, average interval based on 1.0 mean supplemental injections through 1 year in 3E10 vg/eye arm.

Durability Remains the Priority for Retina Doctors & Patients: Long-term Disease Control is Still the #1 Unmet Need

ASRS Preferences and Trends (PAT) Survey 2025

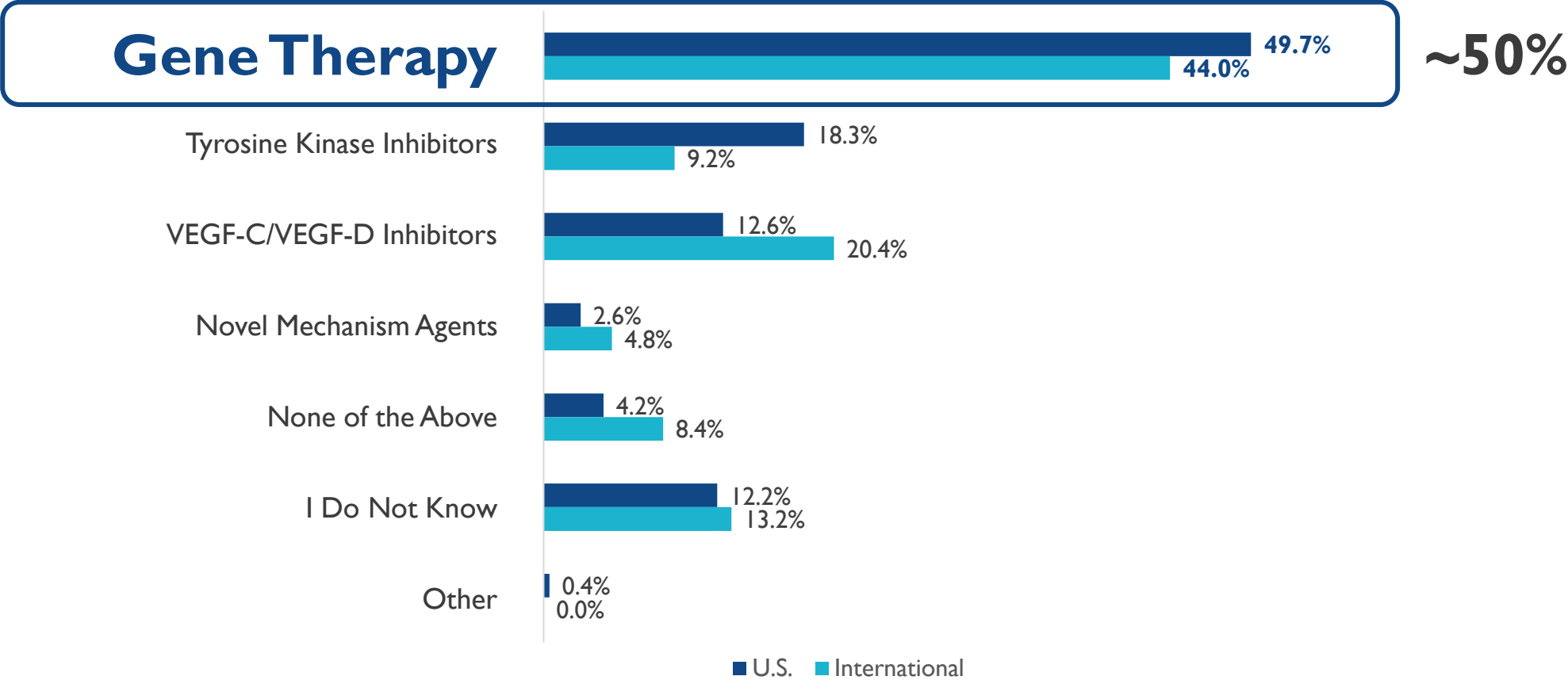
Which factors are most important to you when selecting anti-VEGF agent?



Hahn P, ed. ASRS 2025 Preferences and Trends Membership Survey. Chicago, IL. American Society of Retina Specialists; 2025

Gene Therapy is the Most Exciting Pipeline Treatment: Highest Potential to Achieve True Continuous Disease Control

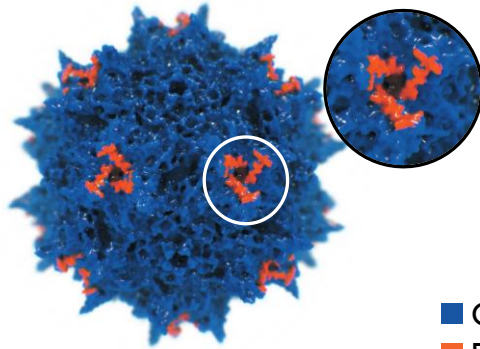
ASRS Preferences and Trends (PAT) Survey 2025
Which pipeline treatment for wet AMD excites you most?



Hahn P, ed. ASRS 2025 Preferences and Trends Membership Survey. Chicago, IL. American Society of Retina Specialists; 2025

4D-I50 is Designed as Backbone Therapy to Provide Safe & Continuous Disease Control with Lifelong Anti-VEGF Expression Potential

R100 Capsid



■ Capsid base
■ Peptide insertions

- ✓ Robust delivery to multiple retinal layers
- ✓ Low doses and minimal inflammation potential



Anti-VEGF Transgenes



Aflibercept
(VEGF Trap)

- ✓ >64 million doses administered WW since launch*



VEGF-C RNAi

- ✓ Enhanced aflibercept expression in preclinical studies¹

4D-I50 Backbone Therapy Target Profile

Single, in-office IVT Injection

Predictable prophylactic
steroid eyedrop taper

Potential for lifelong
durability²

*Regeneron data on file. 1. Calton et al. *Invest Ophthalmol Vis Sci* 2024;65:1. 2. Based on 4DMT and other AAV-based retinal gene therapies.

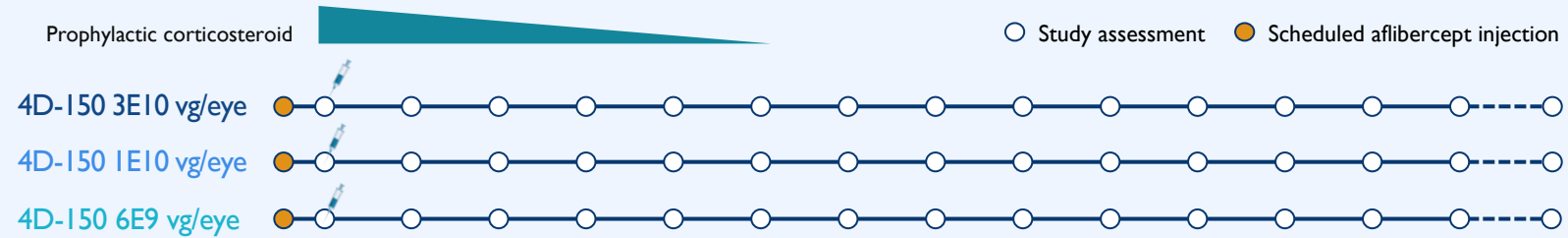
4D-I50 Wet AMD Development Program: Comprehensive Strategy Studying Increasingly Early-Stage Populations



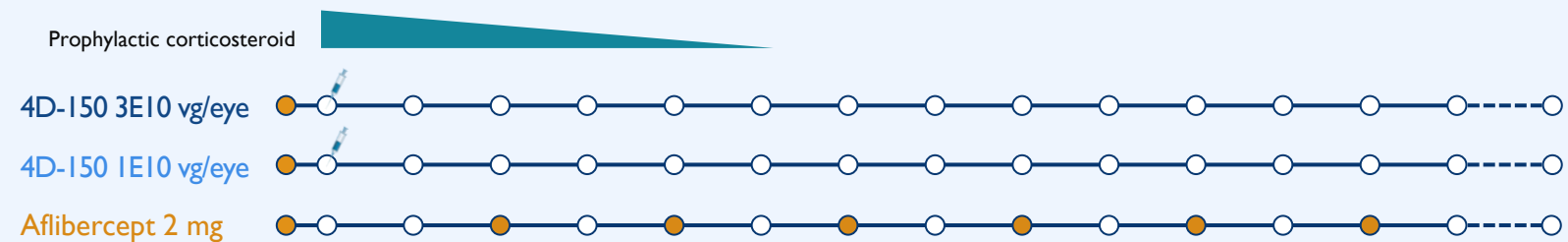
*Phase 3 dose. **≤0.5 years with previous treatment.

Wet AMD Phase I/2 Schemas

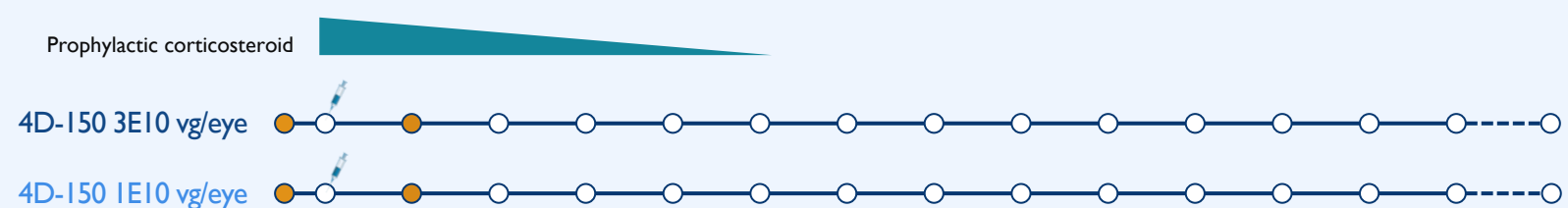
Phase I Dose Exploration



Phase 2a Dose Expansion (randomized)



Phase 2b Population Extension



Supplemental Injection Criteria

Reference Values*

Average of Week -1 and
Day 1

Disease Activity

BCVA: Loss of ≥ 10 letters
attributable to retinal fluid,

OR

CST: Increase of ≥ 75 μm

OR

New vision-threatening
hemorrhage due to wet
AMD per investigator

*BCVA and CST.

CST, central subfield thickness; BCVA, best corrected visual acuity

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

4D-I50 Demonstrated Transformative Treatment Burden Reduction Through 2 Years in Multiple Wet AMD Patient Populations

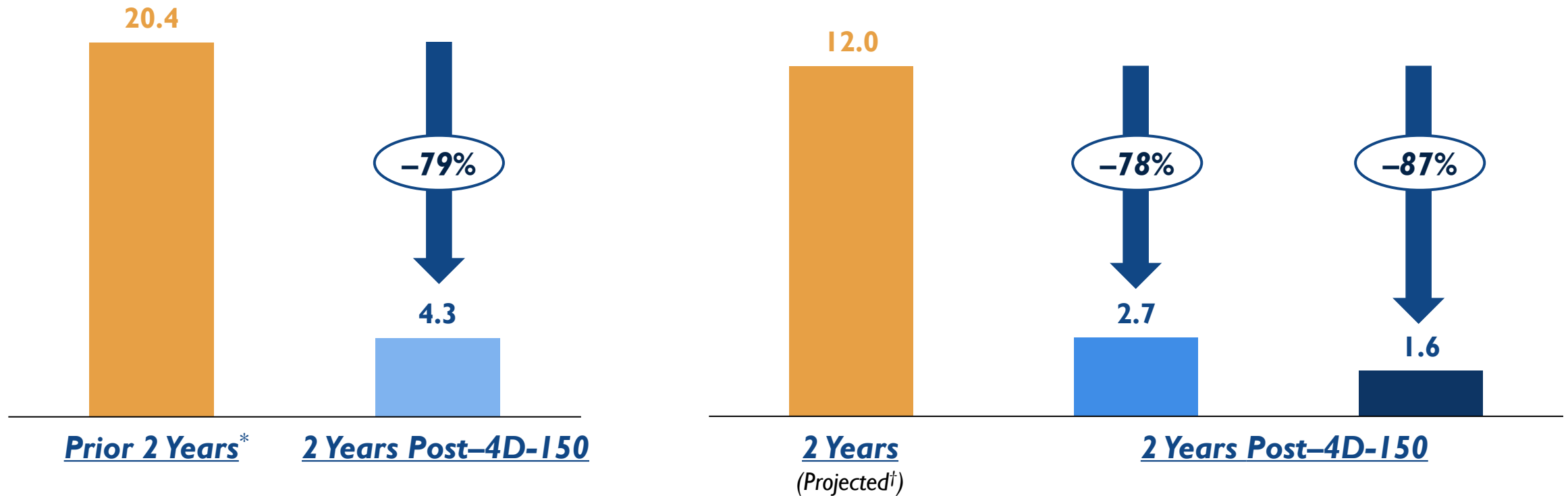
Phase 3 Dose (3E10 vg/eye): Mean Supplemental Anti-VEGF Injections Required

Severe, Recalcitrant



Broad Disease

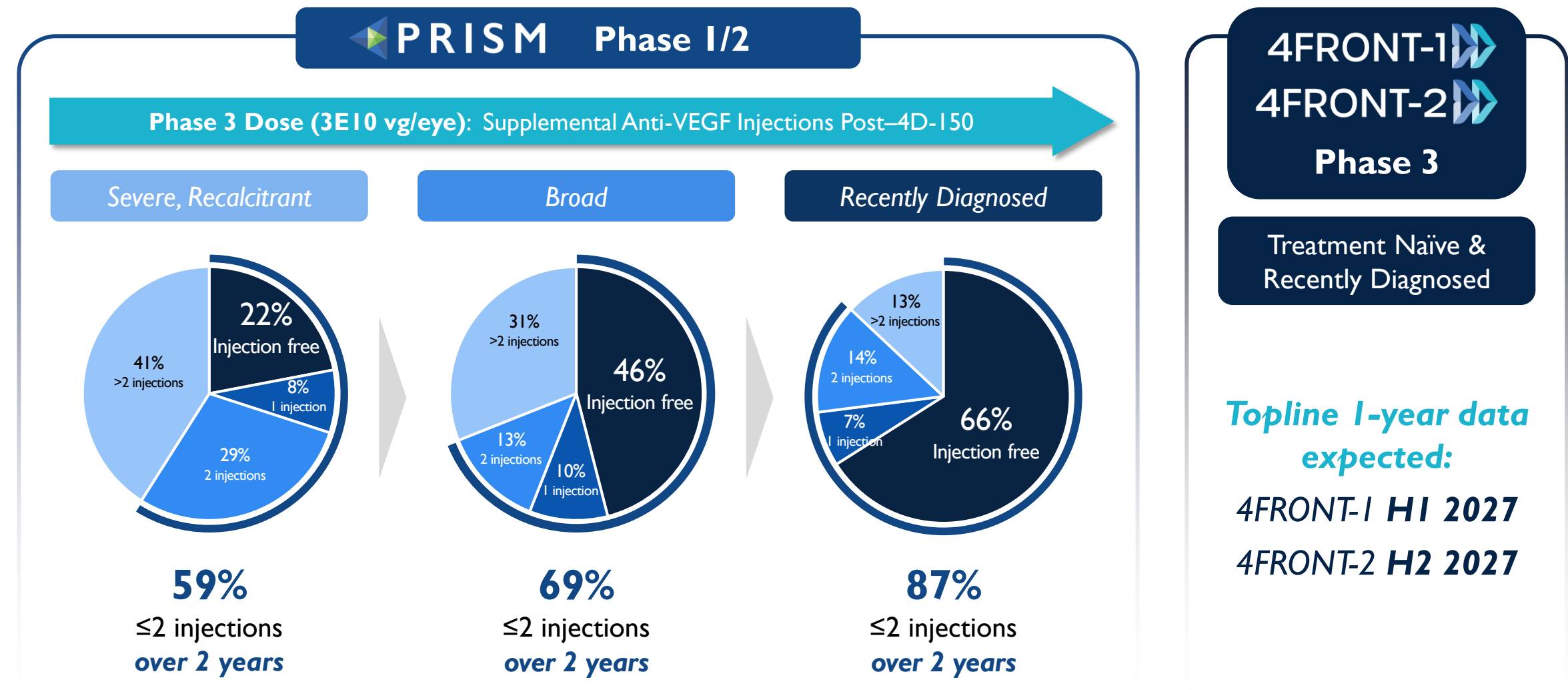
Recently Diagnosed



Data cutoff of May 18, 2026.

*Projected based on mean actual injections of 10.2 in prior year. †Projection based on last loading dose in Phase 2b and approved dosing schedule for aflibercept in wet AMD.

4D-I50 Demonstrated Transformative Treatment Burden Reduction Through 2 Years in Multiple Wet AMD Patient Populations



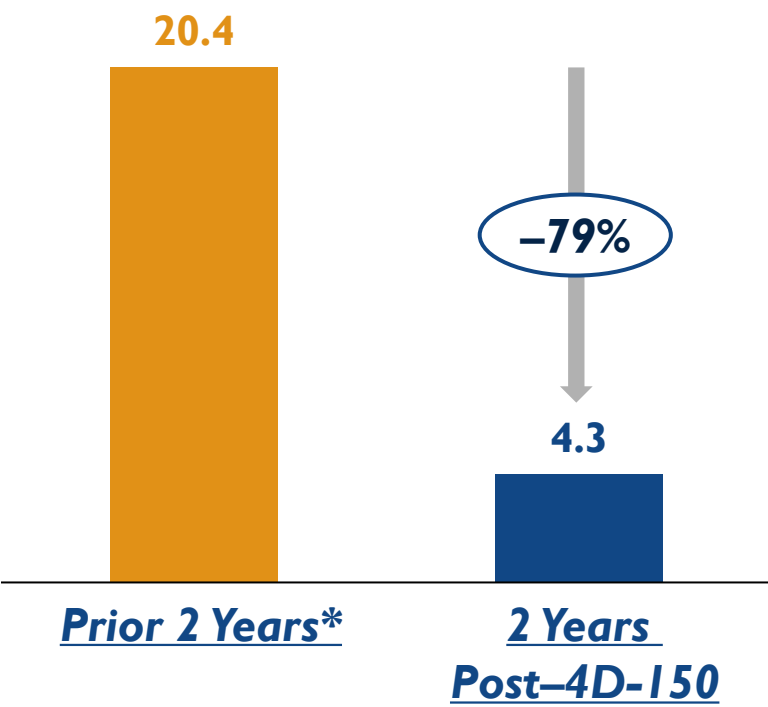
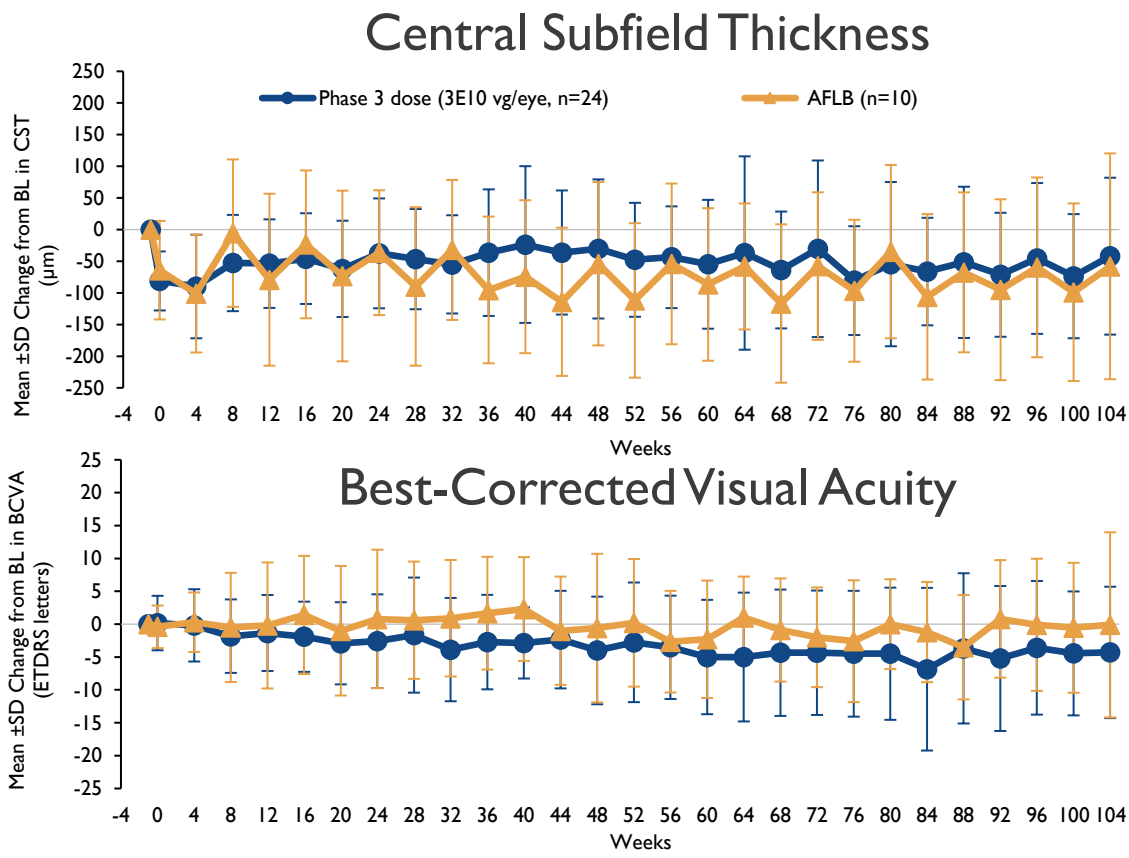
Data cutoff of May 18, 2026.

Results Through 2 Years Post-4D-I50 in a Severe, Recalcitrant Population

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

Anatomy & Visual Acuity 4D-I50 vs. Aflibercept

Treatment Burden Post-4D-I50

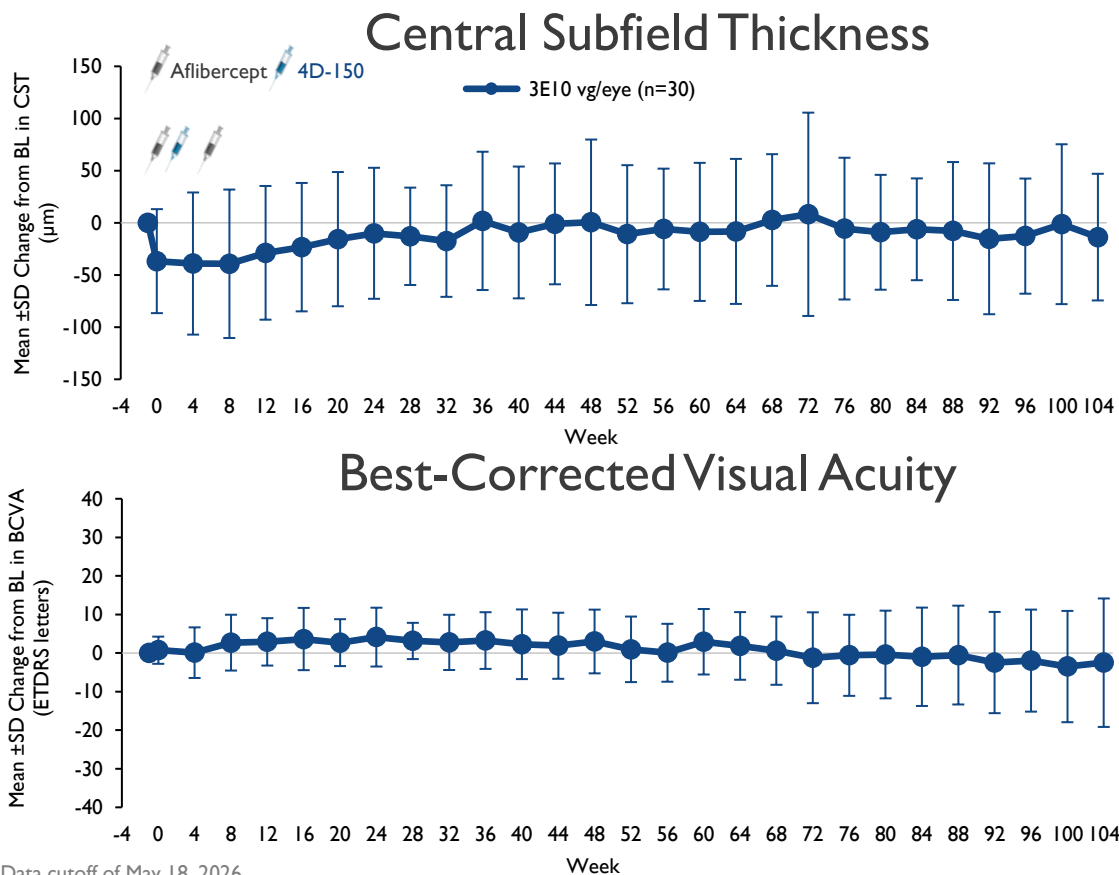


Data cutoff of May 18, 2026.
 CST, central subfield thickness; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; AFLB, aflibercept.
 *Projected based on mean actual injections of 10.2 in prior year.

Results Through 2 Years Post-4D-I50 in a Broad Population

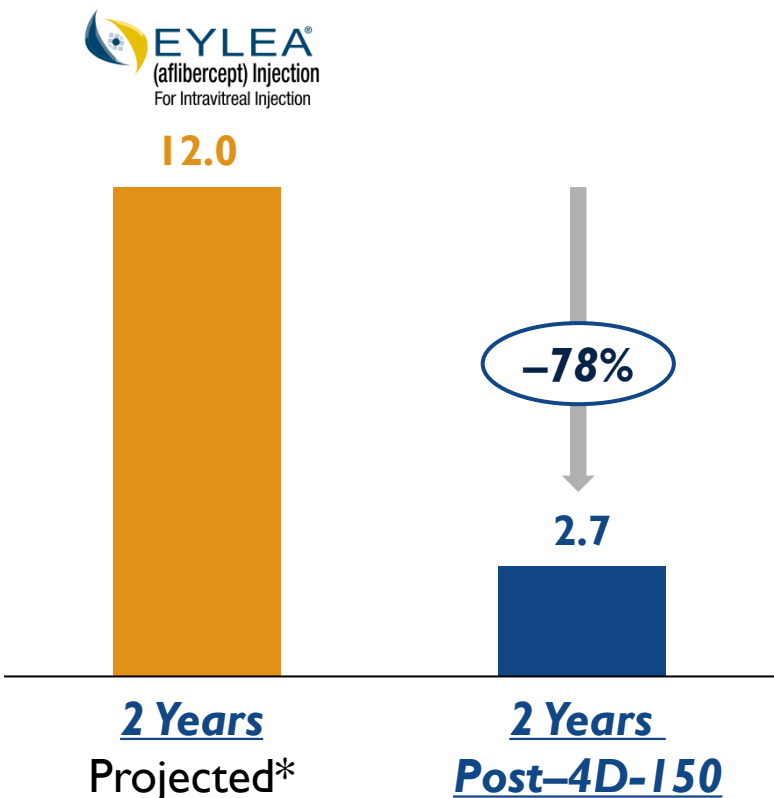
Visual Acuity & Anatomy Stable With Robust Reduction in Treatment Burden

Anatomy & Visual Acuity Post-4D-I50



Data cutoff of May 18, 2026.
 CST, central subfield thickness; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.
 *Projection based on last loading dose in Phase 2b and approved dosing schedule for aflibercept in wet AMD.

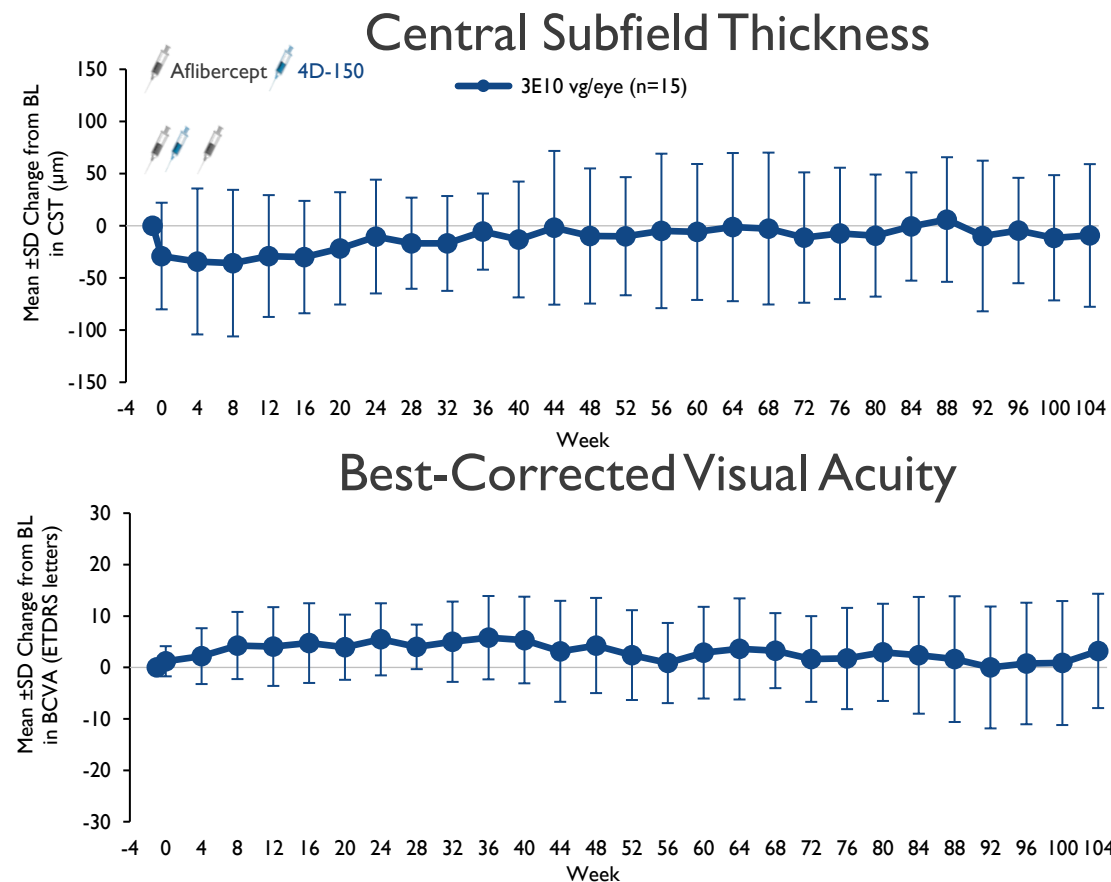
Treatment Burden Post-4D-I50



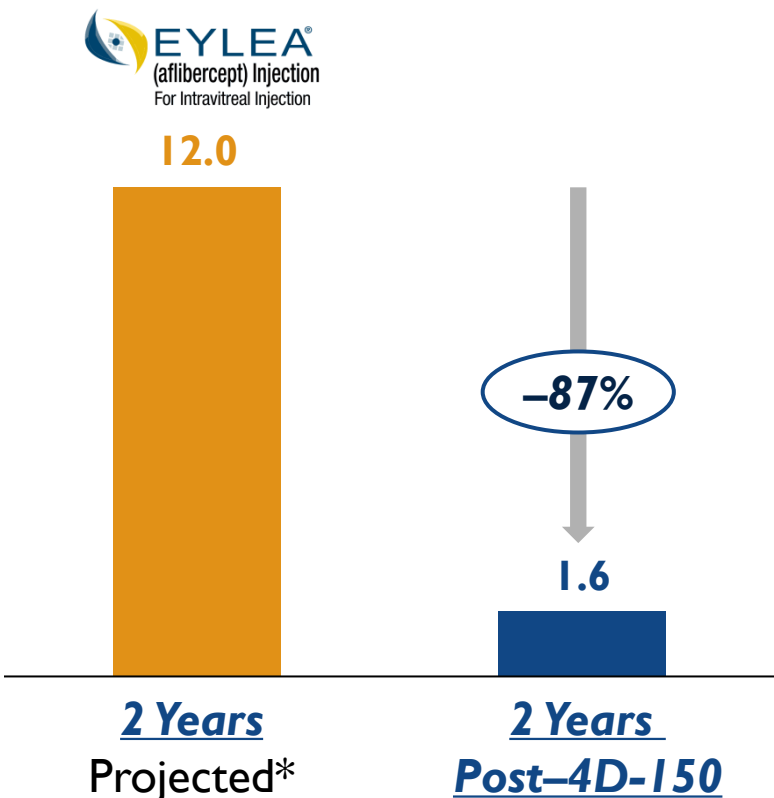
Results Through 2 Years Post-4D-I50 in Recently Diagnosed Population

Visual Acuity & Anatomy Stable With Robust Reduction in Treatment Burden

Anatomy & Visual Acuity Post-4D-I50



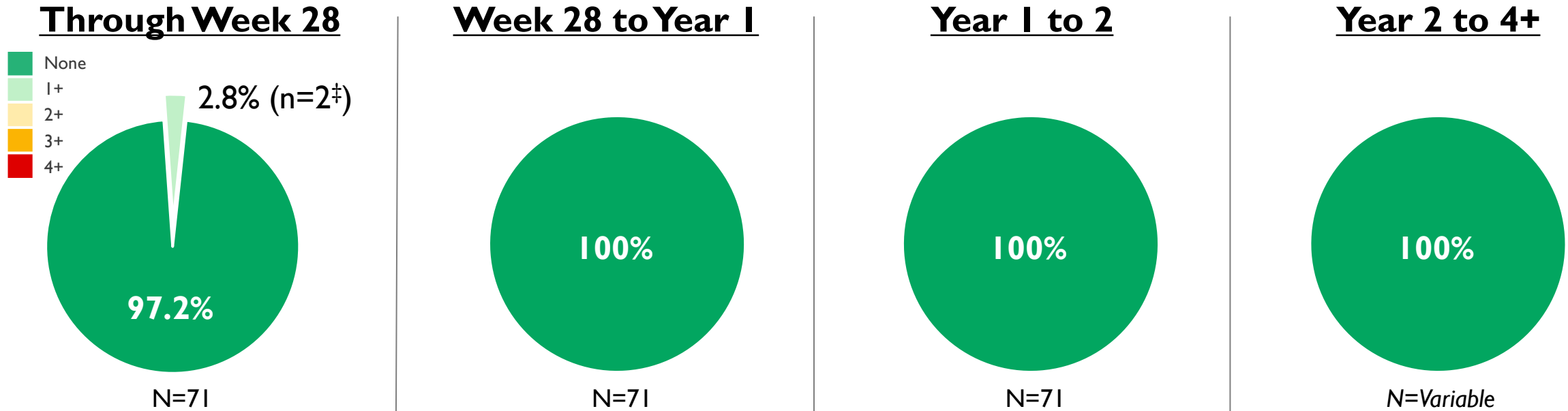
Treatment Burden Post-4D-I50



Data cutoff of May 18, 2026.
CST, central subfield thickness; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study. *Projection based on last loading dose in Phase 2b and approved dosing schedule for aflibercept in wet AMD.

Wet AMD: Consistent and Predictable Safety To-date in Phase 1/2

Highest SUN/NEI Score[†] with 4D-150 Phase 3 Dose, 3E10 vg/eye (N=71)



- No 4D-150–related serious adverse events
- No 4D-150–related hypotony, endophthalmitis, occlusive/non-occlusive retinal vasculitis, or choroidal effusions

Data cutoff of May 18, 2026.

[†]4D-150–related. [‡]1+ VC cell in 1 patient at Week 4 & 1 patient Week 28.

NEI, National Eye Institute; SUN, Standardization of Uveitis Nomenclature.

Global 4FRONT Phase 3 Wet AMD Program Summary

Primary Objective	Noninferiority in mean change in BCVA from baseline to Week 52 for a single injection of 4D-I50 vs. aflibercept 2mg (Q8W) after 3 loading doses
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4FRONT-1

North America
N=480
100% Treatment naïve

✓ **Enrollment completed, N=523 randomized**



4FRONT-2

Global
N=480
≥60% Treatment naïve
*Up to 40% Previously treated**

✓ **Enrollment completed, expect N>500 randomized**

✓ **Regulatory alignment:**

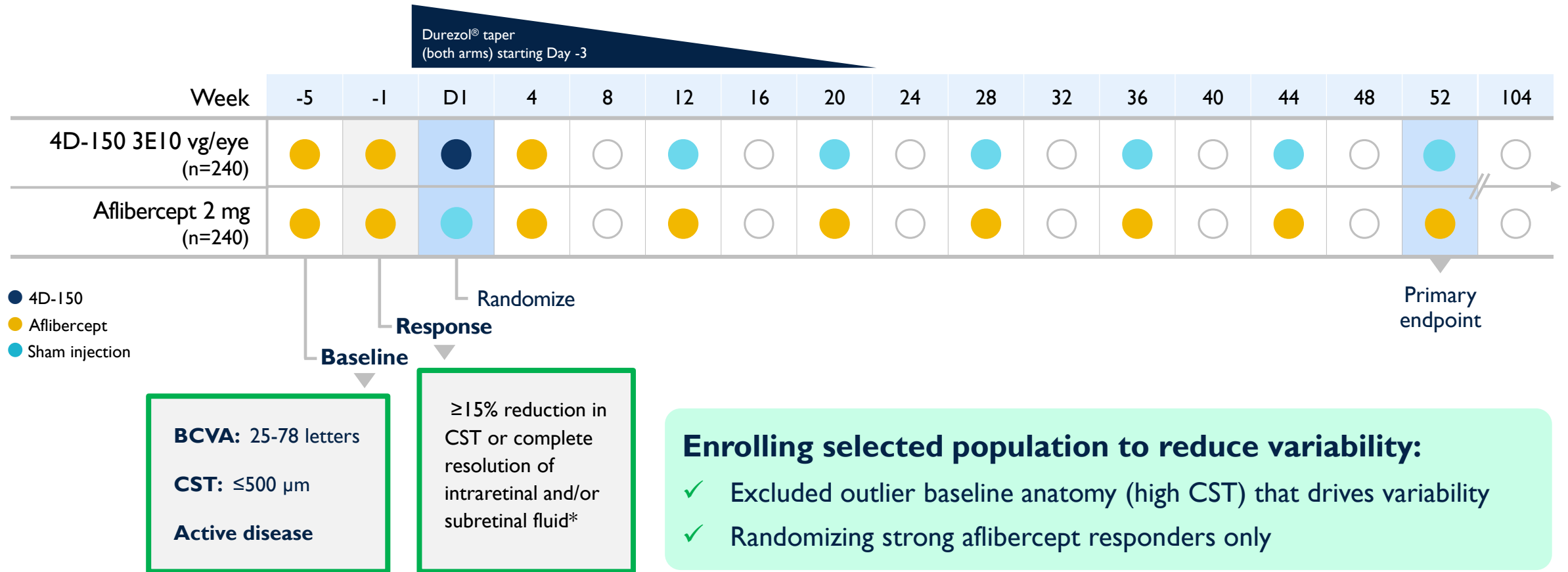
- FDA RMAT designation
- EMA PRIME designation
- Japan PMDA interactions

✓ **Robustly powered for global approval standards (~4 letter noninferiority margin)**

*1-4 prior injections, diagnosed within 6 months.
RMAT, Regenerative Medicine Advanced Therapy; PRIME, Priority Medicines; PMDA, Pharmaceuticals and Medical Devices Agency.

Global 4FRONT Phase 3 Trial Design: Enrolling an Optimized Population

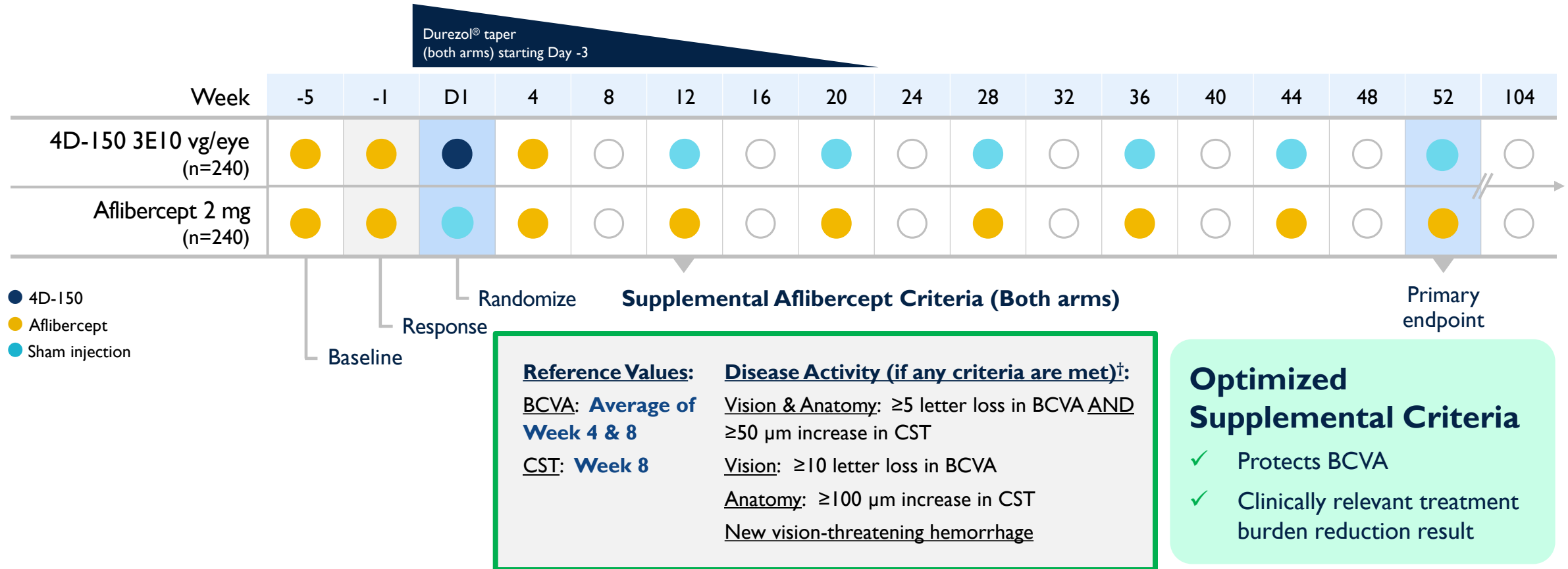
Global, Multicenter, Randomized, Double Masked, Aflibercept Q8W Comparator Controlled Studies



*Determined by SD-OCT and confirmed by an independent Reading Center.

Global 4FRONT Phase 3 Trial Design: Studying Clinically Relevant Endpoints

Global, Multicenter, Randomized, Double Masked, Aflibercept Q8W Comparator Controlled Studies



*Determined by SD-OCT and confirmed by an independent Reading Center. †PI discretion not allowed.

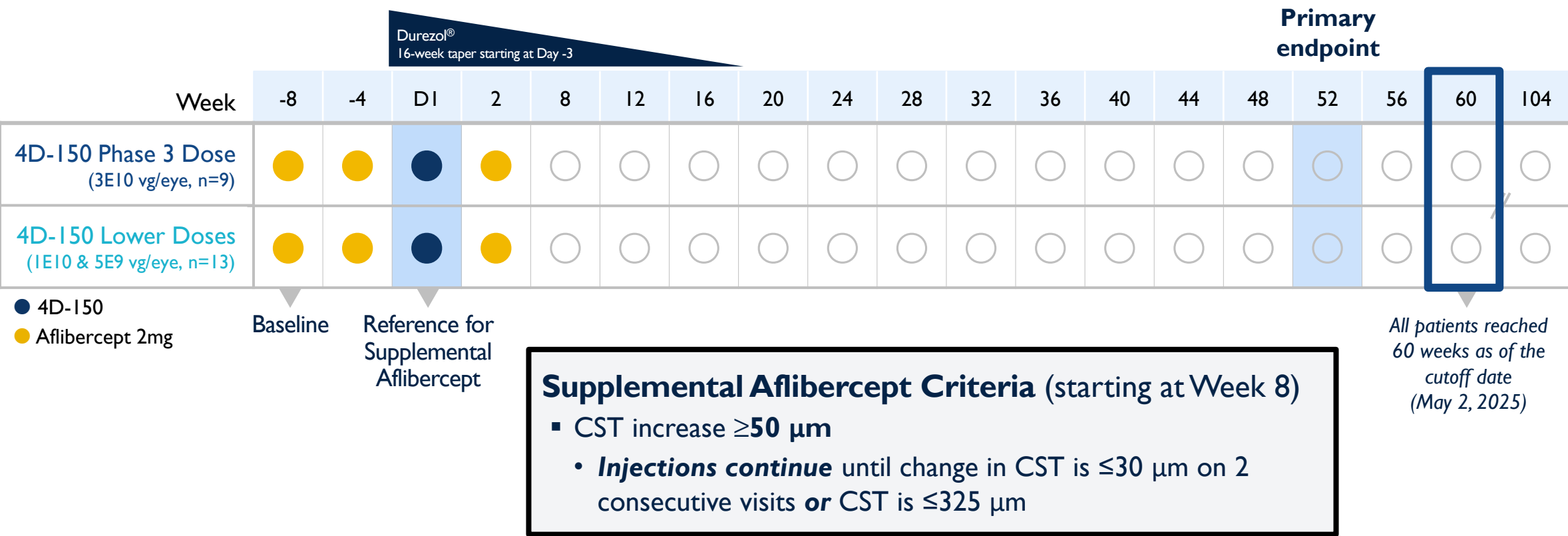
SPECTRA Enrolled DME Patients with Focus on Safety & Dose Selection

Key Eligibility Criteria

Diagnosis within 2 years, CST $\geq 350 \mu\text{m}$ (includes treatment naïve)

Confirmed anti-VEGF response (CST decrease $\geq 40 \mu\text{m}$ at Week -1 versus Week -8)

- Assessed by SD-OCT and confirmed by independent reading center.



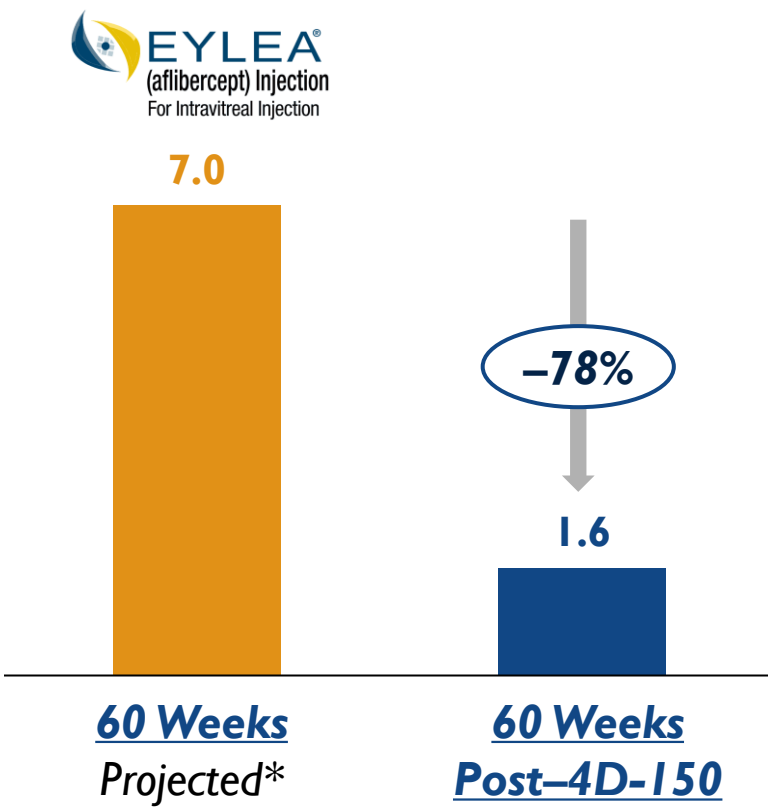
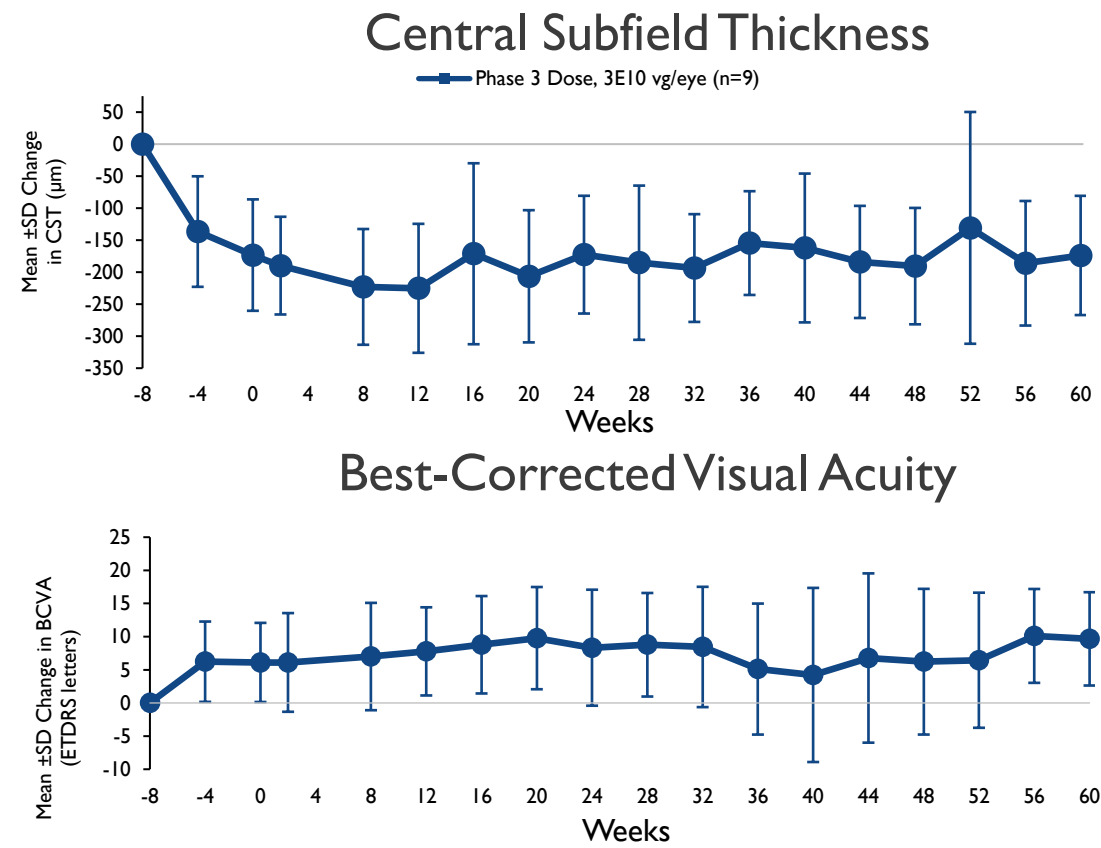
CST, central subfield thickness: defined as thickness of 1mm area from ILM to BM; DME: Diabetic Macular Edema; VEGF: Vascular Endothelial Growth Factor Receptor; vg/eye: viral genomes/eye.

Results Through 60-weeks Post-4D-I50 in DME

Visual Acuity & Anatomy Stable With Robust Reduction in Treatment Burden

Anatomy & Visual Acuity 4D-I50

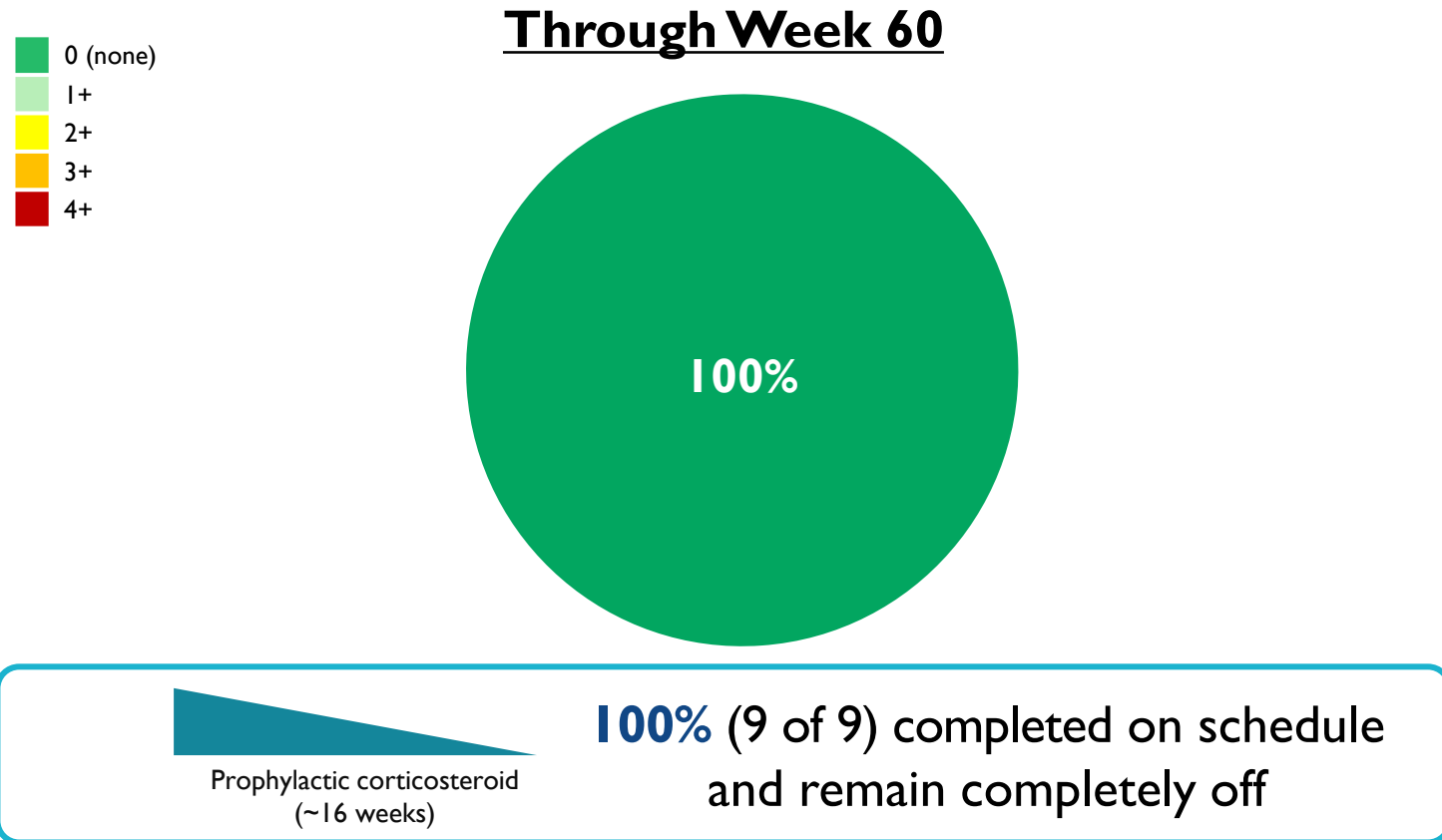
Treatment Burden Post-4D-I50



Data cutoff as of May 2, 2025.
CST: Central Subfield Thickness; SD: Standard Deviation. BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study. *Projection based on approved dosing schedule post-loading for aflibercept in DME.

DME: Consistent & Predictable Safety Data To-date

Highest SUN/NEI Score with 4D-I50 Phase 3 Dose, 3EI0 vg/eye (N=9)



Data cutoff as of May 2, 2025.

NEI: National Eye Institute; SUN: Standardization of Uveitis Nomenclature.

Commercial Model: Designed for Seamless Adoption & Global Scalability



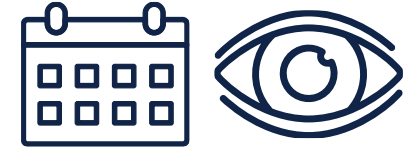
GLOBAL SCALABILITY

- **Manufacturing** scalability
- **Favorable COGS** margin
- **Efficient commercial infrastructure in U.S.** to reach ~2,500 retina specialists (<100 field reps)
- **Otsuka** infrastructure in APAC



PAYERS

- **Unique value proposition** aligns incentives to long-term disease control and **vision protection**
- **Buy & bill model** fit (U.S.)
- **Flexible pricing** enabled by low COGS



PRACTICE WORKFLOW & ECONOMICS

- **In-office routine** IVT dosing
- **Standard refrigeration**
- **Practice economics enhanced**
- **Clinic capacity increased**

Exclusive License Agreement with Otsuka Pharmaceutical for Development & Commercialization of 4D-I50 in Asia-Pacific Region



4D-I50 APAC License

- **\$85M** *upfront*
- **At least \$50M** *cost sharing expected over next three years*
- **Up to \$336M** *in potential regulatory and commercial milestones*
- **Tiered, double-digit** *royalties on net sales in Otsuka territory*

✓ Complementary Strengths:

- **4DMT** expertise in AAV genetic medicine, retina product development and manufacturing
 - **Otsuka** global pharma with expertise in APAC regulatory strategy & execution, and commercialization
- ✓ 4DMT retains full development and commercialization rights for 4D-I50 outside the APAC region
 - ✓ 4DMT continues to **lead global Phase 3 clinical development and manufacturing**
 - ✓ Upfront proceeds and cost reimbursement expected to support **global Phase 3 clinical trial in DME and retina pre-commercial activities**
 - ✓ APAC territory represents **~10% of global retinal anti-VEGF market**

Key Catalysts: Poised for Strong Clinical Data & Phase 3 Execution

Milestones followed by Topline Phase 3 Data

Wet AMD

- ✓ **Feb 2026:** 4FRONT-1 Phase 3 enrollment complete
- ✓ **Jun 2026:** 4FRONT-2 Phase 3 enrollment complete
- ✓ **Jul 2026:** PRISM Phase 2b 2-year data
- **H1 2027:** 4FRONT-1 Phase 3 topline data
- **H2 2027:** 4FRONT-2 Phase 3 topline data

Diabetic Macular Edema

- **Q3 2026:** Finalize global Phase 3 design
- **Q3 2026:** Initiate global Phase 3 trial
- **H2 2026:** SPECTRA Trial 2-year data

\$458M Cash*, Runway Expected into H2 2028

*Cash, cash equivalents and marketable securities as of March 31, 2026.



4D-710



Potential Durable, Variant-Agnostic,
Disease-Modifying Treatment for
Cystic Fibrosis Lung Disease

Cystic Fibrosis Lung Disease: High Unmet Need Despite Modulators

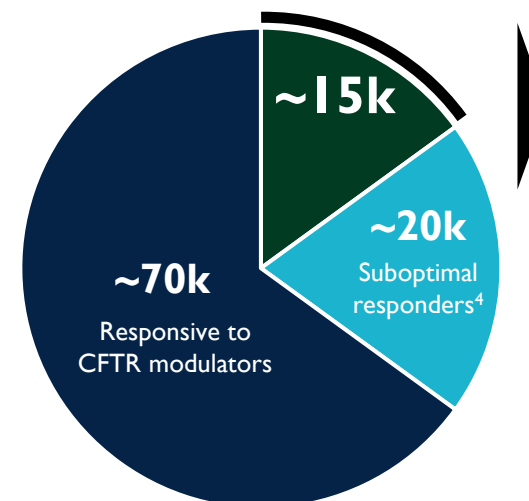
Lung Disease Burden



Burdensome Daily Supportive Care:
Airway clearance (~100 mins),
inhaled antibiotics & bronchodilators

- **Persistent symptoms** with cough, shortness of breath, infections & reduced exercise tolerance
- Pulmonary exacerbations, often requiring **hospitalization and IV antibiotics**
- **Lung transplantation** as a last resort
- **Median survival** (pre-modulator era): ~40 years¹

CF Epidemiology^{2,3}



~105,000 People
with CF in 94 Countries

Ineligible or Intolerant
to CFTR
modulators

AEROW

*Initial study population
evaluating 4D-710 as
monotherapy*

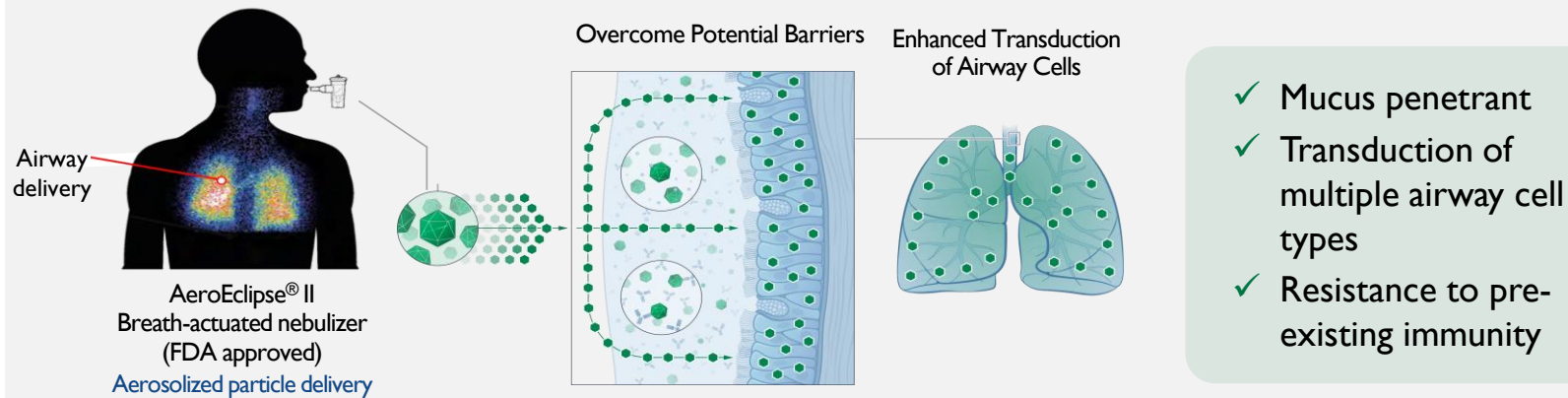
**CFTR Modulator
Market Size**

**~\$12 Billion
(2025)⁵**

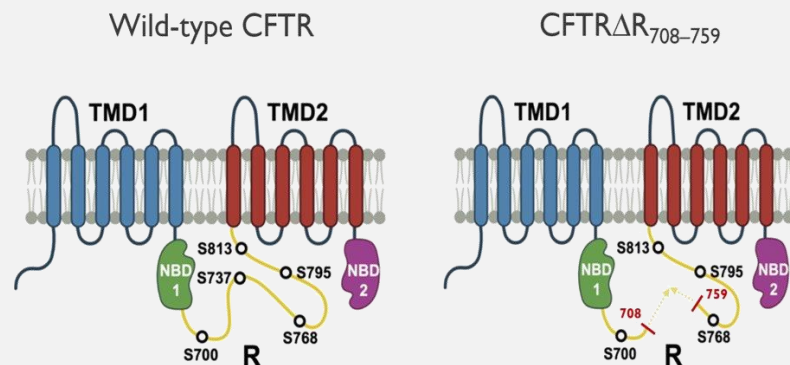
1. Ramsey & Welsh. *Am J Respir Crit Care Med* 2017;195(9):1092–9. 2. Guo J et al. *Journal of Cystic Fibrosis* 2022; 21:456–62. 3. Cystic Fibrosis Foundation. 4. Based on assumptions derived from Middleton, 2019 and CFF registry analysis. 5. Vertex Pharmaceuticals FY 2025 financial results.

4D-710 Design: Durable, Redosable, Variant-agnostic Disease-modifying Therapy for CF Lung Disease

Novel AAV Vector: A101



Payload: *CFTR*Δ*R* Transgene



- Partial deletion in the regulatory domain
- **Normal channel structure, function and regulation**^{1,2}
- Corrected disease phenotypes in CF pig model³

4D-710

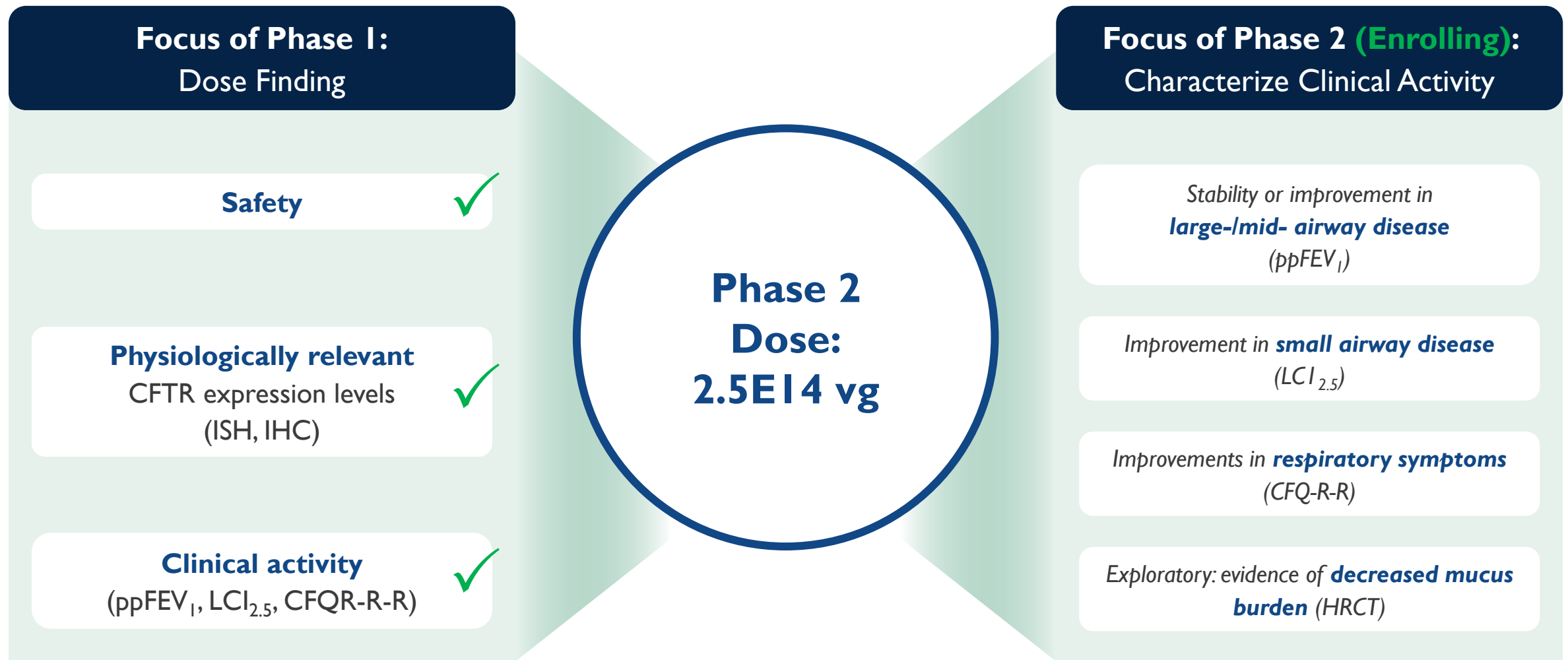


Therapeutic Objective:

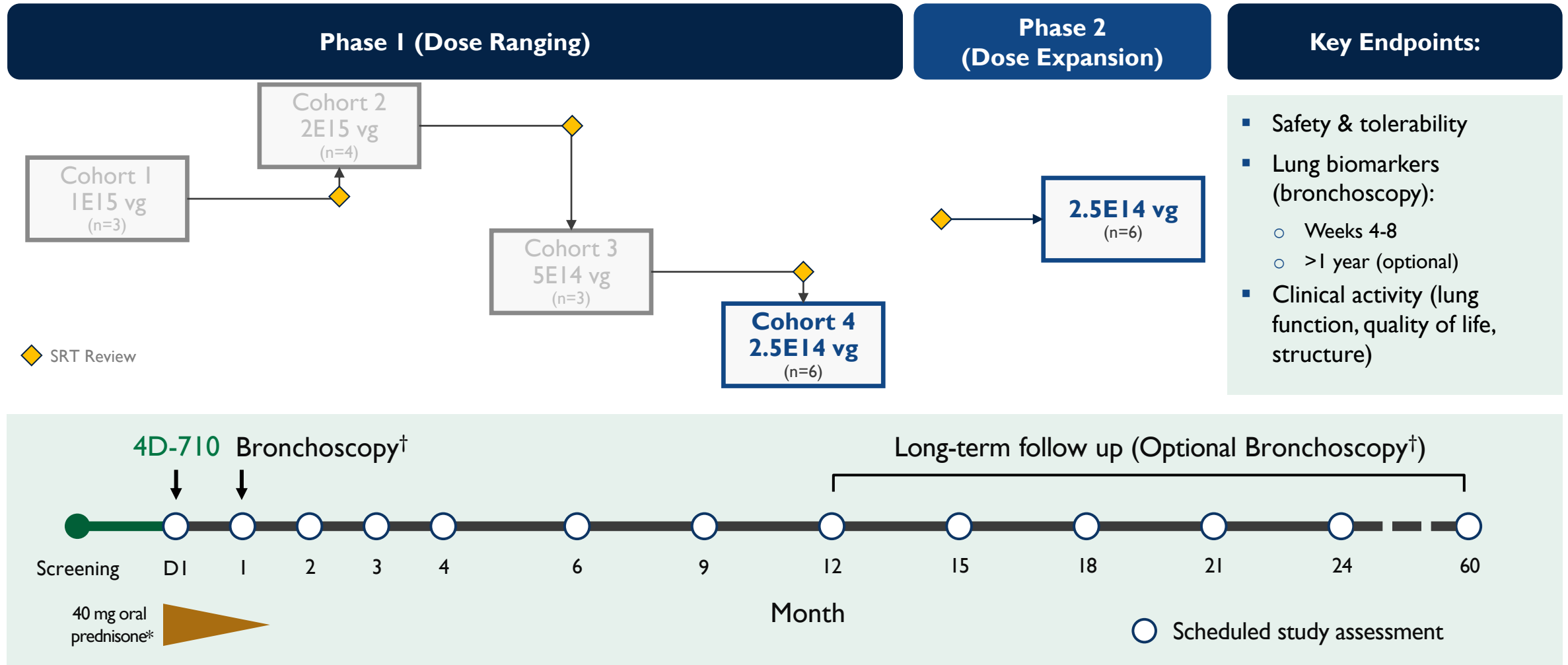
Durable, redosable, variant-agnostic disease-modification via introduction of functional CFTR to lung airway cells

1. Ostedgaard et al. *PNAS* 2002;99:3093-8; 2. Calton et al. *AJRCMB* 2015; 3. Steines et al. *JCI Insight* 2016.

Dose Selection Framework for Further Development of 4D-710



Protocol Amended with Novel Lung Endpoints to Enhance Clinical Activity Assessments, Additional Biopsy to Assess Durability



*28-day taper. †Endobronchial biopsy (4D-710 transgene and protein expression). ppFEV₁, percent predicted forced expiratory volume in 1 second; SRT, Safety Review Team; MBW, Multiple Breath Washout; LCI_{2.5}, Lung Clearance Index at 2.5% of starting concentration; HRCT, High Resolution Computed Tomography.

AEROW Clinical Trial: Lower Dose Cohorts 3 & 4 (N=9)

Demographics & Baseline Characteristics

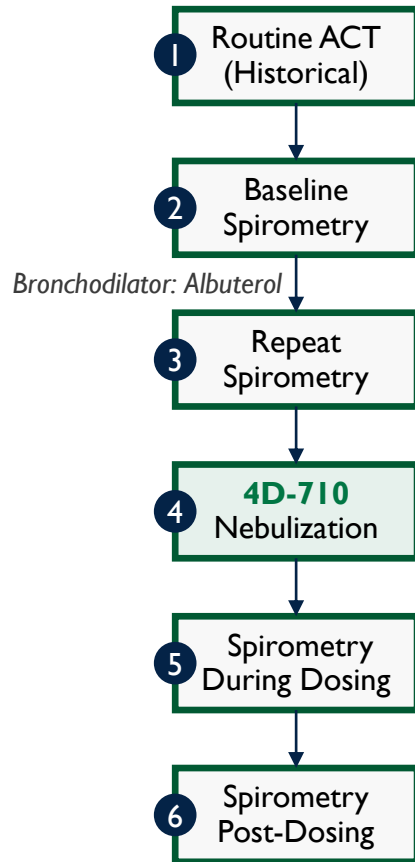
	Cohort 3: 5E14 vg			Cohort 4: 2.5E14 vg					
Participant Number	1	2	3	1	2	3	4	5	6
Age, y	42	40	34	26	54	37	56	33	37
Sex	Female	Female	Male	Male	Female	Female	Male	Male	Male
CFTR mod. status	Intolerant	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible	Ineligible
CFTR Variants	F508del/ R751L	4209TGTT>AA/ 3120+1G>A	Q220X/ Q493X	c.2184_2185insA/ c.2184_2185insA	1471delA/ 1717-1G>A	W1282X/ H1079P	3659delC/ 5T	S466X/ 1342-1delG	G542X/ W1282X
ppFEV ₁	100	77	62	58	89	50	90	76	63
LCI _{2.5} (Normal: <7)	N/A	14.7	18.2	14.3	13.2	N/A	N/A	15.8	13.0
CFQ-R-R score (0-100)	72	78	44	28	72	56	93	89	61

Impairment: **Mild/Normal**, **Moderate/Severe/Abnormal**.

CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R-R, Cystic Fibrosis Questionnaire–revised (respiratory domain); FEV₁, forced expiratory volume in 1 second.

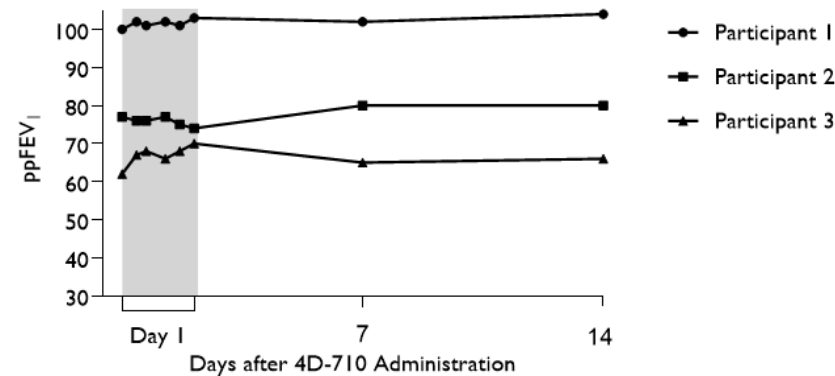
4D-710 Safety & Tolerability Day 1-14: Well-Tolerated in Lower Dose Cohorts with Transient & Generally Mild AEs Typical of Nebulized Therapies

Day 1 Dosing Activities



ppFEV₁

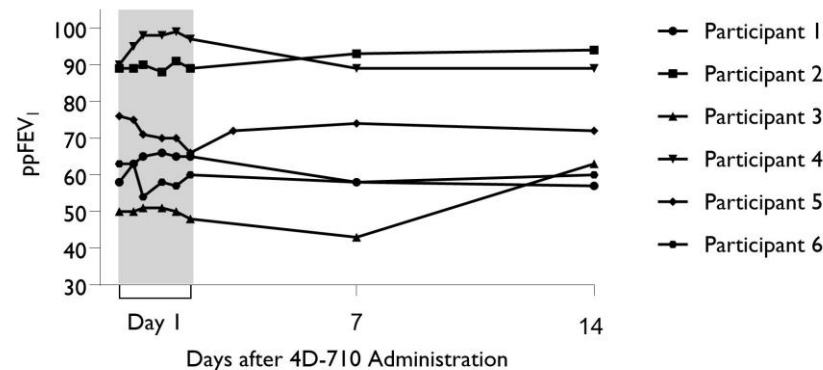
5E14 vg
Admin. Time
~90 Mins



4D-710-Related AE

- Participant 1: **throat irritation** after dosing (Grade 1, ~5 sec), increased **productive cough** (Grade 1, Day 4-13)

2.5E14 vg
Admin. Time
~45 Mins



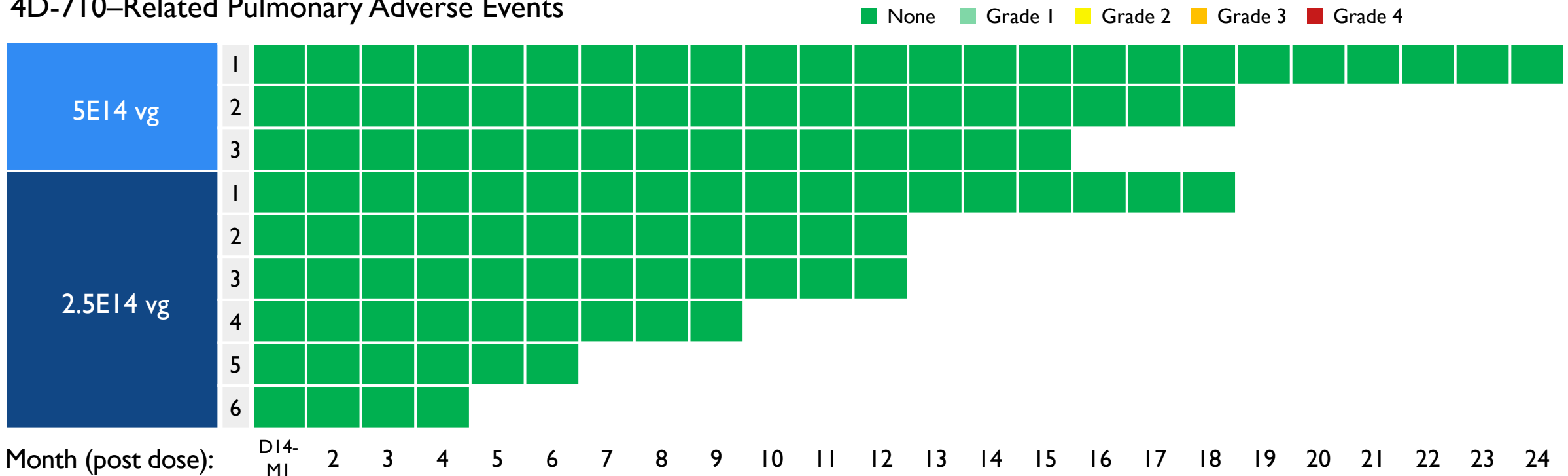
- Participant 5: increased **cough and lightheadedness** during dosing (Grade 1, resolved Day 1 without intervention), **chest tightness and decrease in FEV₁** (Grade 2, Day 1-8)

AE, Adverse Event; ACT, Airway Clearance Technique.

4D-710 Safety & Tolerability: Well-Tolerated in Lower Dose Cohorts

No Pulmonary 4D-710–related AEs After Day 14

4D-710–Related Pulmonary Adverse Events

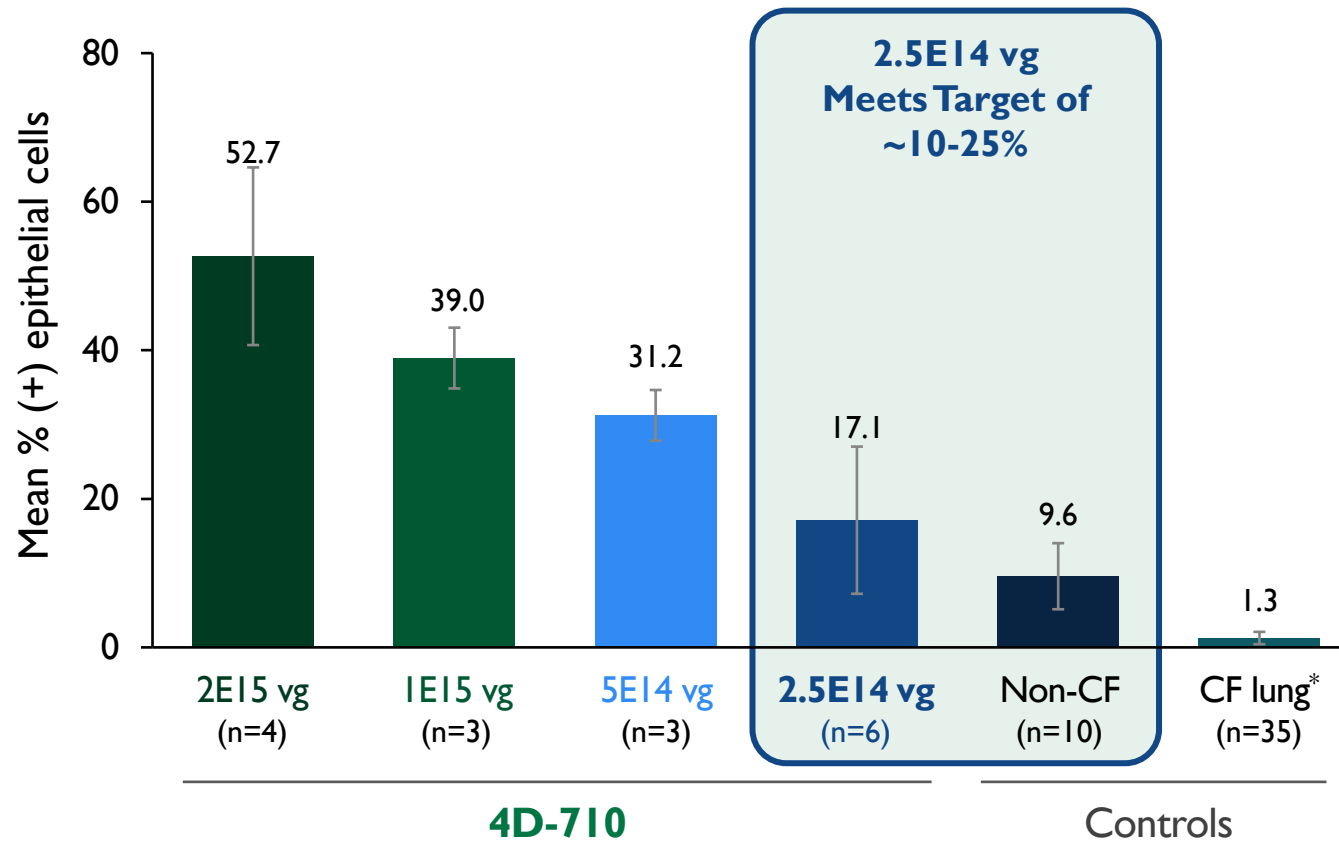


- Higher dose cohorts (1E15 & 2E15 vg): NO new related AEs since last update (up to 3.5 years of follow up)
- Non-Pulmonary 4D-710–Related AEs:
 - 5E14 vg (Participant 3): 1) Mental Fogging: Grade 2, started Day 24 and resolved Day 35; 2) Stuttering: Grade 2, started Day 25 and resolved Day 35
 - 2.5E14 vg (Participant 5): 1) Elevated AST & GGT: Grade 1, identified at 1M visit (Day 36) and resolved by 2M visit (Day 57). Participant with history of elevated LFTs at baseline

AEs from 2E15 and 1E15 doses previously disclosed.

Dose-dependent *CFTR* Transgene RNA Expression Following 4D-710 Administration: Cohort 4 (2.5E14 vg) Meets Target Expression Profile

CFTR RNA (ISH): Airway Epithelial Cells

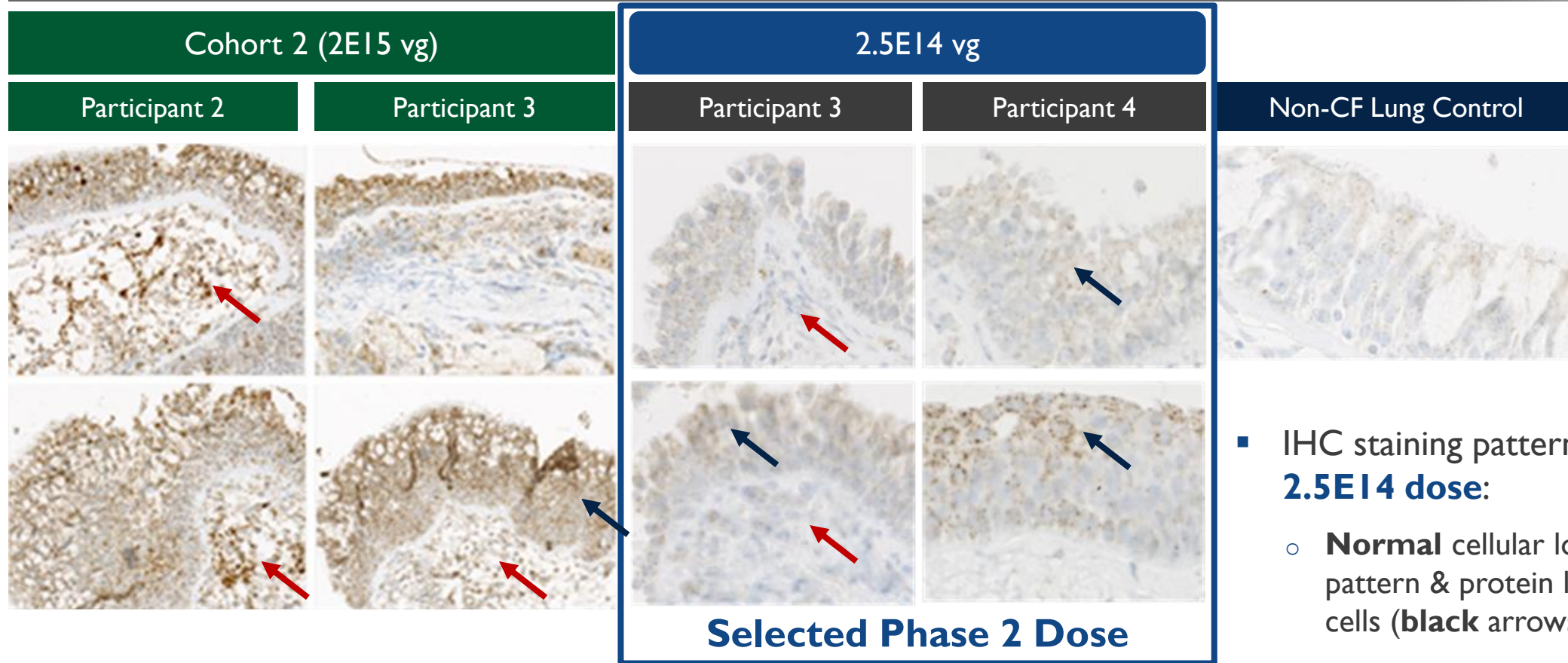


- Dose-dependent *CFTR* mRNA expression in airway cells
- **2.5E14 vg dose (Cohort 4) meets target expression profile^{1,2}**

4D-710 biopsies analyzed Day 28 – Day 56

CFTR, cystic fibrosis transmembrane conductance regulator; ISH, *in situ* hybridization. Quantification by Visiopharm® AI machine Learning analysis. *Attempts to genotype commercial CF samples yielded results for 13/35 samples; of these, a majority were $\Delta F508$ homozygous mutations. 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.

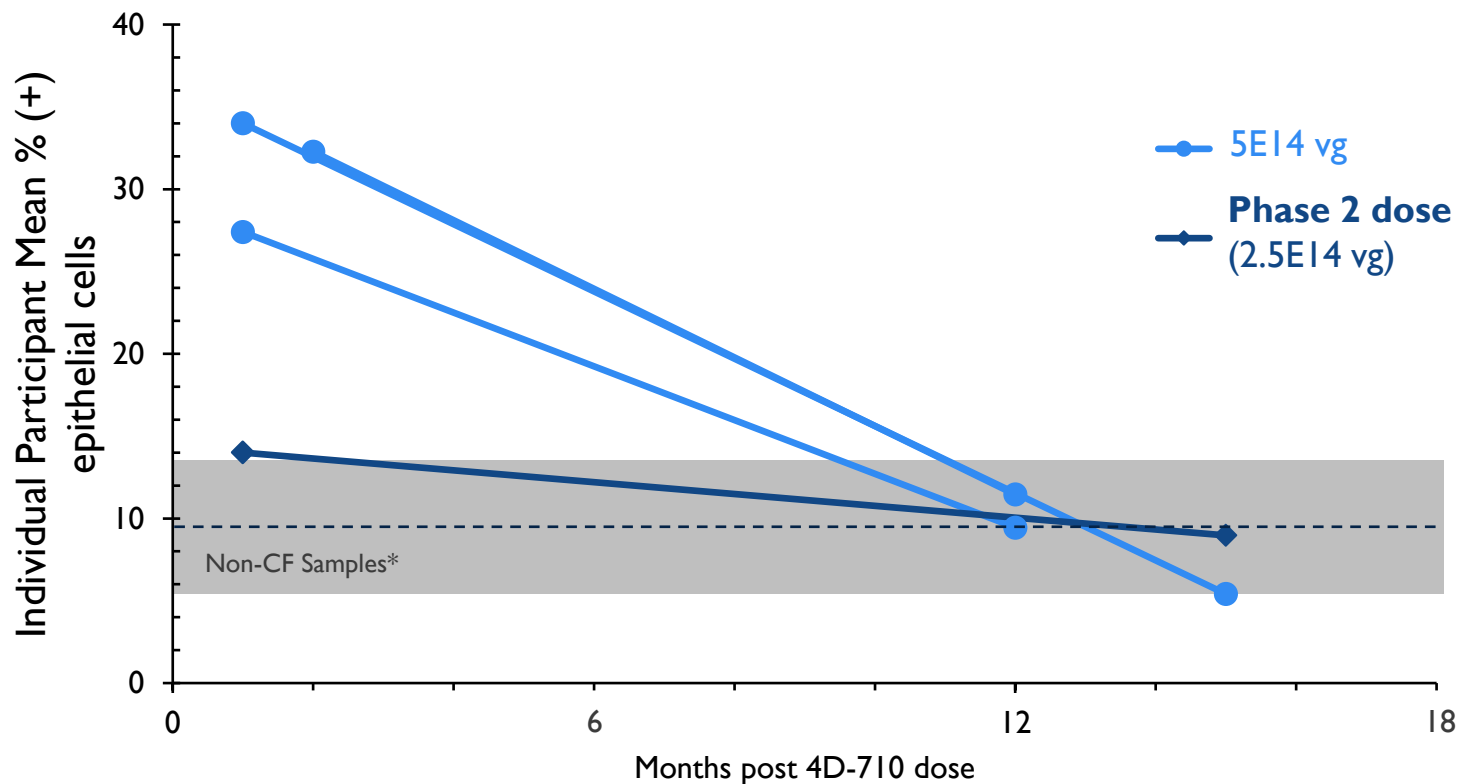
CFTR Protein Expression Meets Target Expression Pattern in Airway & Interstitial Areas at 2.5E14 vg Dose (Cohort 4)



- IHC staining pattern improved at **2.5E14 dose**:
 - **Normal** cellular localization pattern & protein levels in airway cells (**black** arrows)
 - **Minimal/no protein** in interstitial areas of lung (**red** arrows)

Durability of 4D-710–mediated CFTR Expression in Airway Biopsies: Persistent within Target Therapeutic Range through Over 1 Year

Durability of 4D-710–Mediated *CFTR* Δ R Expression (ISH):
Mean % of Airway Epithelial Cells (+) in Individual Patients with Optional Paired Biopsies



Population & Methods

Participants in 1E15, 5E14, and 2.5E14 vg dose cohorts elected to a bronchoscopy to collect paired lung biopsies at ≥ 1 -year post-4D-710 dosing. 5E14, 2.5E14 vg data shown here (*1E15 vg data in appendix*)

Key Findings

Durable expression with levels consistent with the non-CF % (+) epithelial cells and expression levels over 1 year

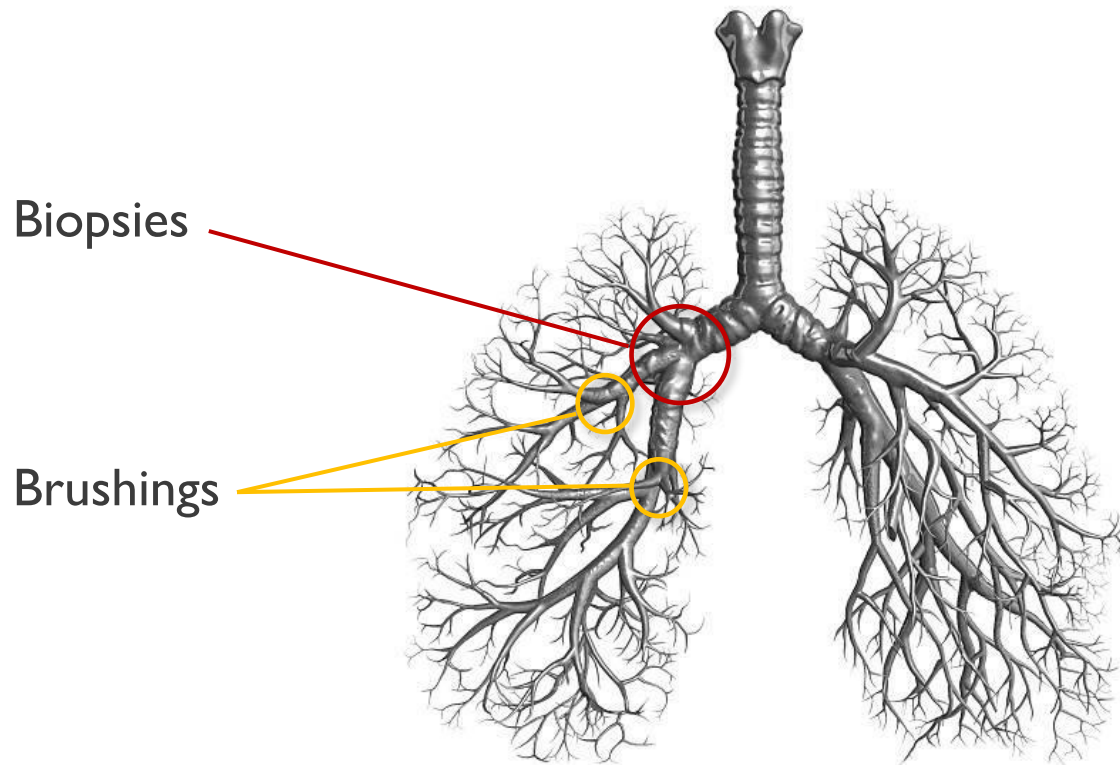
Next Steps

Collect additional paired biopsy data alongside clinical activity measures with focus on Phase 2 dose to inform redosing strategy

Quantification by Visiopharm® AI machine Learning analysis. *Mean ($\pm$ SD) in non-CF samples = 9.6% ($\pm$ 4%). CFTR, cystic fibrosis transmembrane conductance regulator; ISH, *in situ* hybridization

Integrated Biomarker & Clinical Endpoint Strategy to Demonstrate Mechanism of Action & Clinical Activity in AEROW Phase I Trial

Lung Tissue Biomarkers



Pulmonary Clinical Activity Endpoints

Larger Airways

- ppFEV₁

Small Airways

- Lung Clearance Index (LCI_{2.5})

New in Lower Dose Cohorts

Pulmonary Symptoms

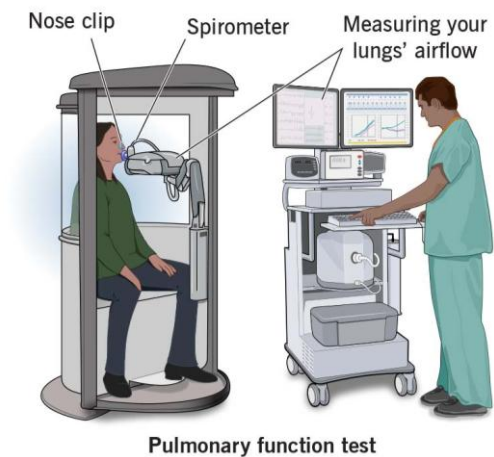
- CFQ-R-R

Structural/Functional Changes

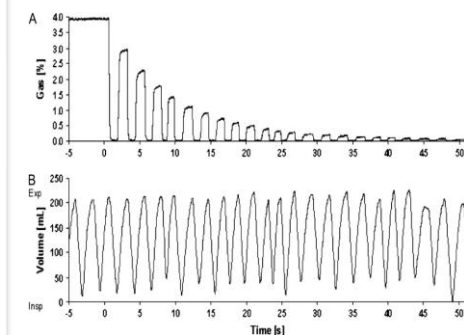
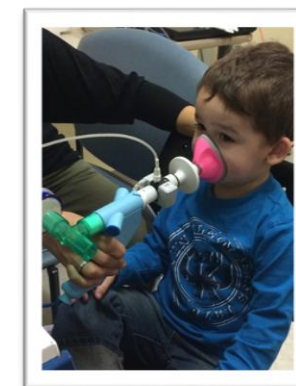
- HRCT (analyses pending)

ppFEV₁, percent predicted forced expiratory volume in 1 second; LCI_{2.5}, Lung Clearance Index at 2.5% of starting concentration; CFQ-R-R, Cystic Fibrosis Questionnaire–revised respiratory domain; HRCT, High Resolution Computed Tomography.

ppFEV₁ & LCI_{2.5}: Complementary Measures of Lung Function



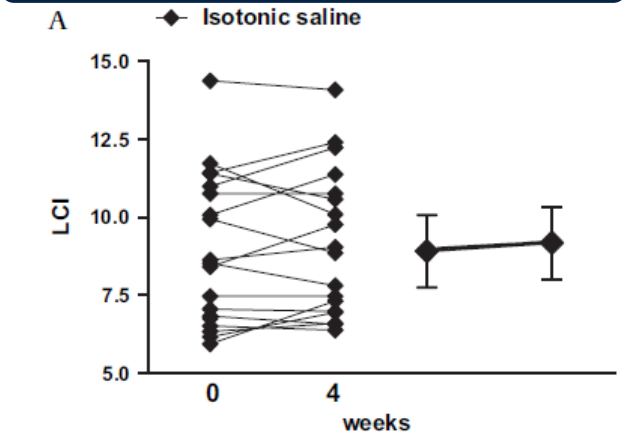
Cleveland Clinic ©2024



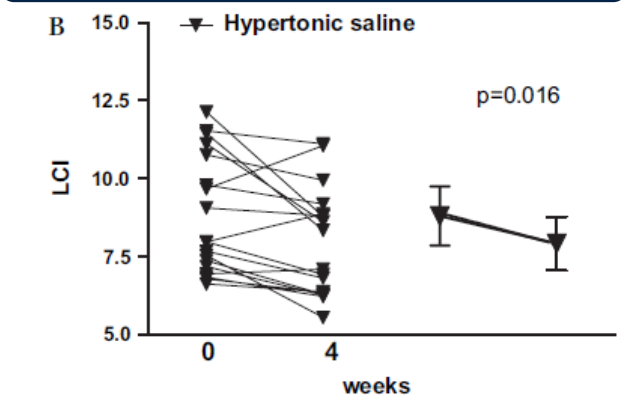
Measure / Endpoint	Spirometry: ppFEV ₁	Multiple Breath Washout: LCI _{2.5}
Measures	Lung restriction/obstruction, marker of larger airway disease	Ventilation inhomogeneity, marker of small airway disease
Effort Dependent	Yes	No
Sensitivity to Early Disease	Low	High
Responsiveness to Intervention	Medium <i>may miss subtle improvement in early/mild disease</i>	High
Correlation to Clinical Outcomes (Survival, Exacerbations, QoL)	Yes	Yes
Regulatory Acceptance	Gold Standard in Adults	EMA Primary in Pediatrics FDA Key Efficacy Endpoint in Pediatrics

LCI_{2.5} Demonstrated Significantly Greater Sensitivity than ppFEV₁ for Treatment Effect: Required <19 Subjects vs ~350

Inactive Control



Modestly Active Treatment



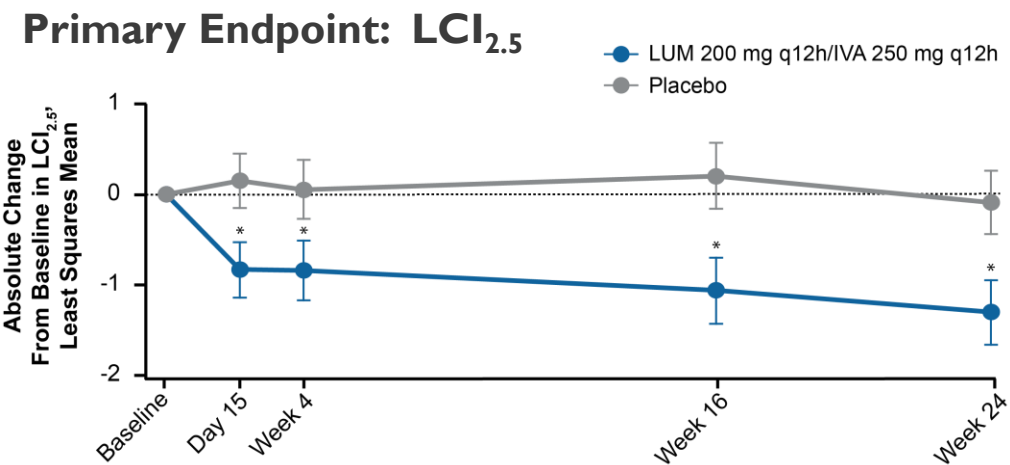
Treatment
effect size:
 1.16 ± 0.94
[0.27, 2.05]
p=0.016

Outcome Analysis	HS vs. IS Treatment Effect*	Required Sample Size†
<u>Spirometry:</u>		
ppFEV ₁	1.8 ± 12.0	351
ppFEF ₂₅₋₇₅	5.3 ± 22.3	141
<u>CFQ-R Questionnaire:</u>		
Respiratory Domain	5.2 ± 14.2	61
<u>Multiple-Breath Washout</u>		
LCI _{2.5}	1.16 ± 0.94 (p=0.016)	≤19

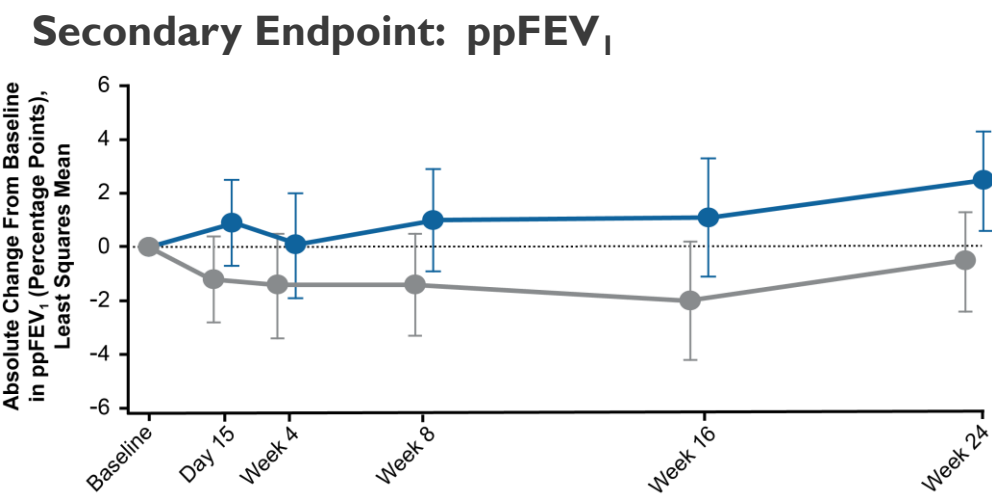
LCI_{2.5} able to detect subtle treatment effects

Amin et.al, Thorax 2010. *Absolute difference for isotonic saline vs hypertonic saline, Values are expressed as means ± SD. †Required number of patients for a crossover trial to achieve 80% power at a 5% significance level.

In Orkambi® Trial in Children, LCI_{2.5} Demonstrated Robust Treatment Response at Every Timepoint vs. Placebo in Contrast to ppFEV₁



Endpoint	Placebo (n=101)	LUM/IVA (n=103)	Treatment Difference vs Placebo
Absolute change in LCI _{2.5} through week 24	0.08 (-0.18 to 0.34)	-1.01 (-1.27 to -0.75)	-1.09 (-1.43 to -0.75) <i>P</i> <0.0001

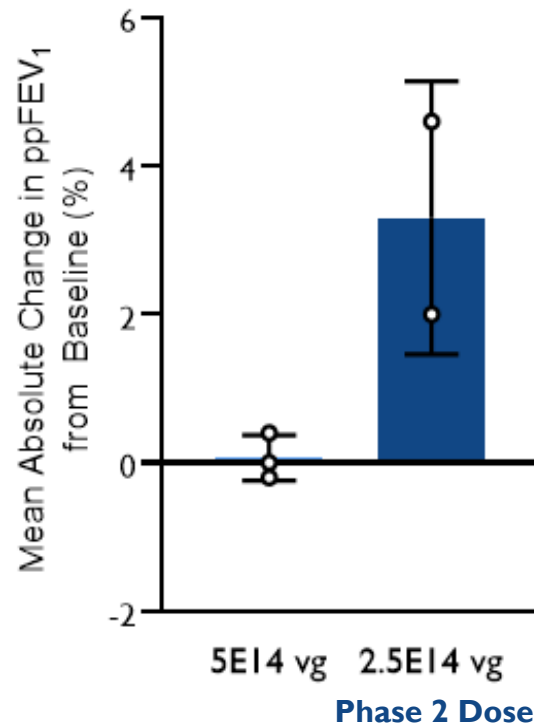


Endpoint	Placebo (n=101)	LUM/IVA (n=103)	Treatment Difference vs Placebo
Absolute change in ppFEV ₁ through week 24	-1.3 (-2.8 to 0.2)	1.1 (-0.4 to 2.6)	2.4 (0.4 to 4.4) <i>P</i> =0.0182

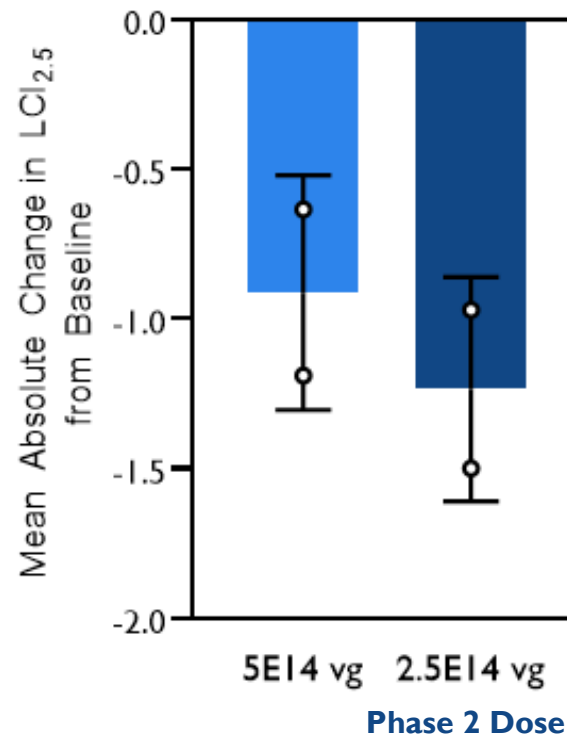
*Ratjen F et al, *Lancet Respir Med* 2017
P≤0.0001 vs placebo; all values in table are least squares mean (95% confidence interval [CI]). LCI, lung clearance index; LUM/IVA, lumacaftor/ivacaftor.

Clinical Activity: Mean Change in ppFEV₁, LCI_{2.5} & CFQ-R-R in Lower Dose Cohorts From Baseline Through 1 Year of Follow-up (Months 3 to 12*)

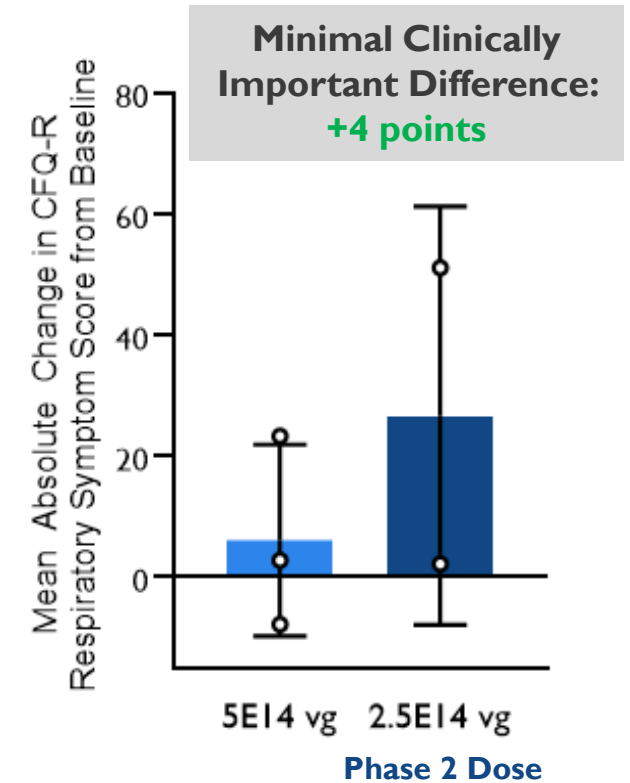
ppFEV₁



LCI_{2.5}



CFQ-R-R



*Post-Hoc analysis of evaluable data: Mean values for each participant calculated from 3M to 12M values, excluding non-evaluable time points with acute pulmonary AEs within 14 days of a study visit. If Month 12 visit was missed or non-evaluable then Month 15 timepoint was used. Note: Analysis for participants in cohort who had at least 12 months of follow-up. Excludes 2.5E14 vg Participant 3.

Phase I Interim Data: Key Takeaways from Lower Dose Cohorts 3 & 4



4D-710

Durable, Redosable, Variant-Agnostic, Disease-Modifying Treatment Potential for People
with CF Lung Disease with
Remaining High Unmet Need

SAFETY DATA: Well Tolerated with 4 to 24 Months follow-up

LUNG FUNCTION: Clinically Meaningful Activity (FEV_1 , $LCI_{2.5}$)

QUALITY-OF-LIFE: Clinically Meaningful Activity (CFQ-R-R)

PHASE 2: Enrollment Underway at Cohort 4 dose level

DURABILITY: 4D-710-mediated CFTR transgene expression through at least 1 year

AEROW Phase I/2 clinical trial & program update expected H2 2026



THANK YOU

5858 Horton Street, Suite 455 | Emeryville, California 94608

(510) 505-2680 | Investor.Relations@4DMT.com

IR.4DMT.com | [LinkedIn](#)

Platform Solution:

~1 Billion Synthetic Capsid Sequences and Competitive Selection in NHP

Step 1:

Create Massive Diversity in Highly Diverse and Distinct Libraries

CONVENTIONAL
NATURALLY
OCCURRING
CAPSIDS

CREATE ~1 **BILLION** SYNTHETIC
AAV CAPSID SEQUENCES BY
DIVERSIFYING THE CAP GENE

HIGHLY DIVERSE AND
DISTINCT 4DMT AAV
CAPSID LIBRARIES

IDENTIFY
DISEASE
TARGET(S)

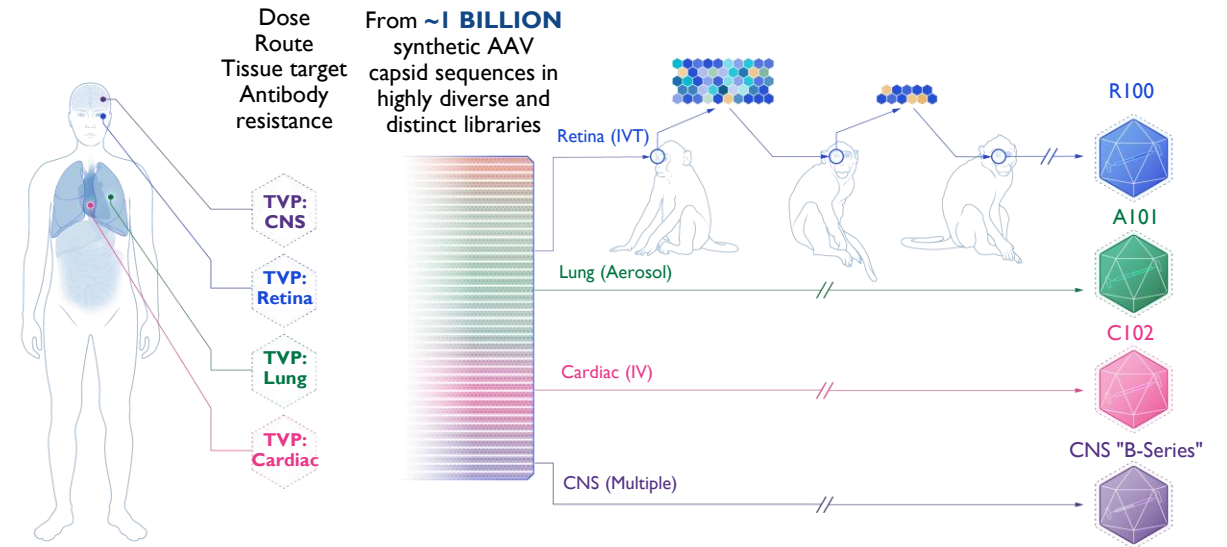
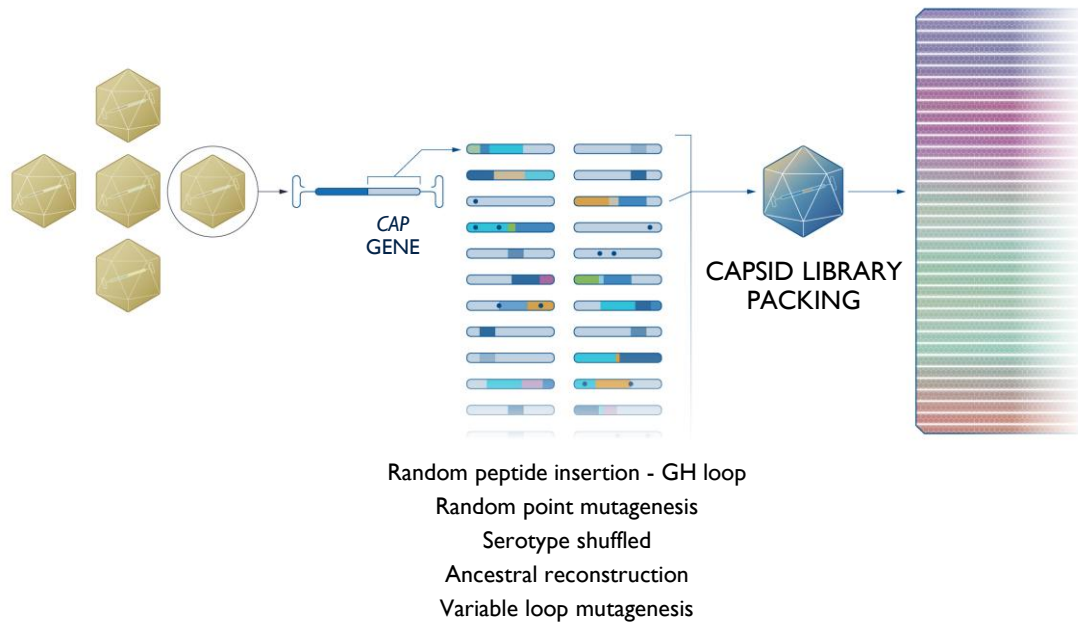
DESIGN
ORGAN(S)-SPECIFIC
**TARGET VECTOR
PROFILE**

PACKAGE
4DMT AAV
LIBRARIES

ADMINISTER
4DMT AAV
LIBRARIES

COMPETITIVE SELECTION*
TARGET VECTOR PROFILE FITNESS

LEAD
VECTORS



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

4FRONT Supplemental Criteria Optimized for Phase 3 Success & Clinically Meaningful Treatment Burden Reduction



Reference Measurement	Post 1 loading dose: ▪ <u>BCVA & CST</u> : Average of Week -1 and Day 1	Post 2-3 loading doses : ▪ <u>BCVA</u> : Average of Week 4 & 8 ▪ <u>CST</u> : Week 8
Vision & Anatomy	None	≥5 letter loss in BCVA AND ≥50 μm increase in CST
Vision Only	≥10 letter loss in BCVA OR	≥10 letter loss in BCVA OR
Anatomy Only	≥75 μm increase in CST OR	≥ 100 μm increase in CST OR
Hemorrhage	Presence of vision-threatening new macular hemorrhage OR	Presence of vision-threatening new macular hemorrhage
PI Discretion	Allowed	Not Allowed