4DMT

Genetic Medicines, Redefined

Corporate Presentation

May 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-150 to Global Commercialization

THERAPEUTIC AREA VECTOR	PRODUCT CANDIDATE	INDICATION	PRE-CLINICAL	PHASE I	PHASE 2	PIVOTAL	BLA FILING	PARTNERS
RETINA **R100** Intravitreal	**4D-150**	**Wet AMD**						Otsuka APAC Rights **4DMT: U.S./EU/ROW**
		DME						
	4D-175	Geographic Atrophy						*Open IND, evaluating strategic funding alternatives*
PULMONOLOGY **A101** Aerosol	**4D-710**	CF lung disease						CYSTIC FIBROSIS FOUNDATION *Fully Funded*
	4D-725	A1AT 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

4DMT

4D-150

Potential Backbone Therapy for Treatment of Retinal Vascular Diseases

Wet Age-related Macular Degeneration (Wet AMD)

Diabetic Macular Edema (DME)

4D-150

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

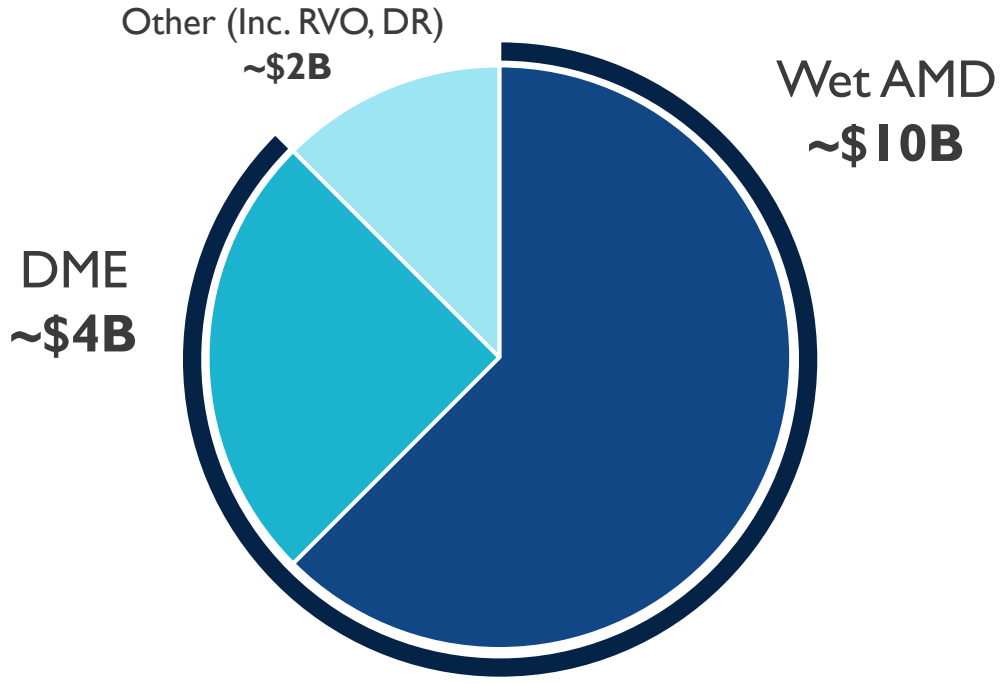
1. **Continuous disease control** enabled by **durable** retinal expression of **aflibercept**
2. **Global Phase 3 program** for Wet AMD & DME
3. **Paradigm-shifting durability** from incremental interval extension to potential **lifelong disease control & vision preservation**

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**

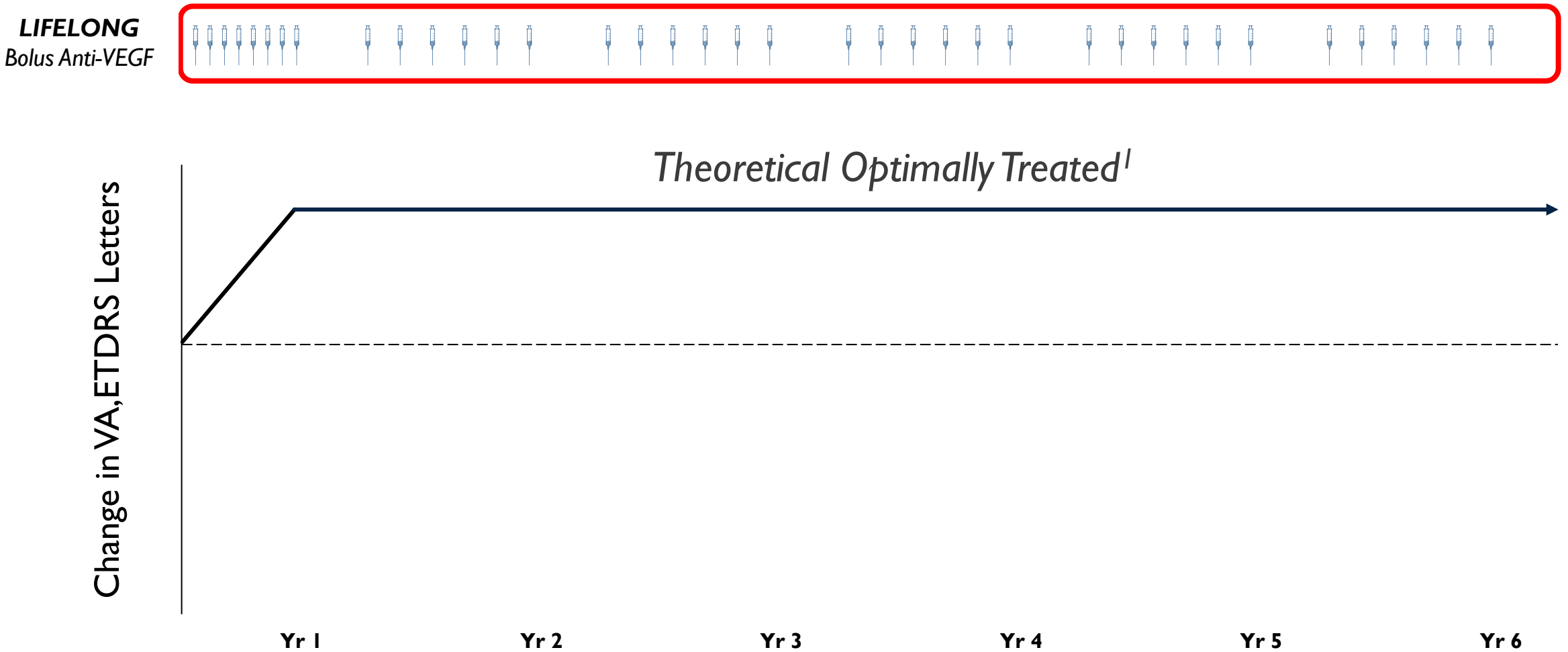
$16B Global Branded Retinal Vascular Disease Anti-VEGF Market (2025E)



Wet AMD + DME: ~$14B

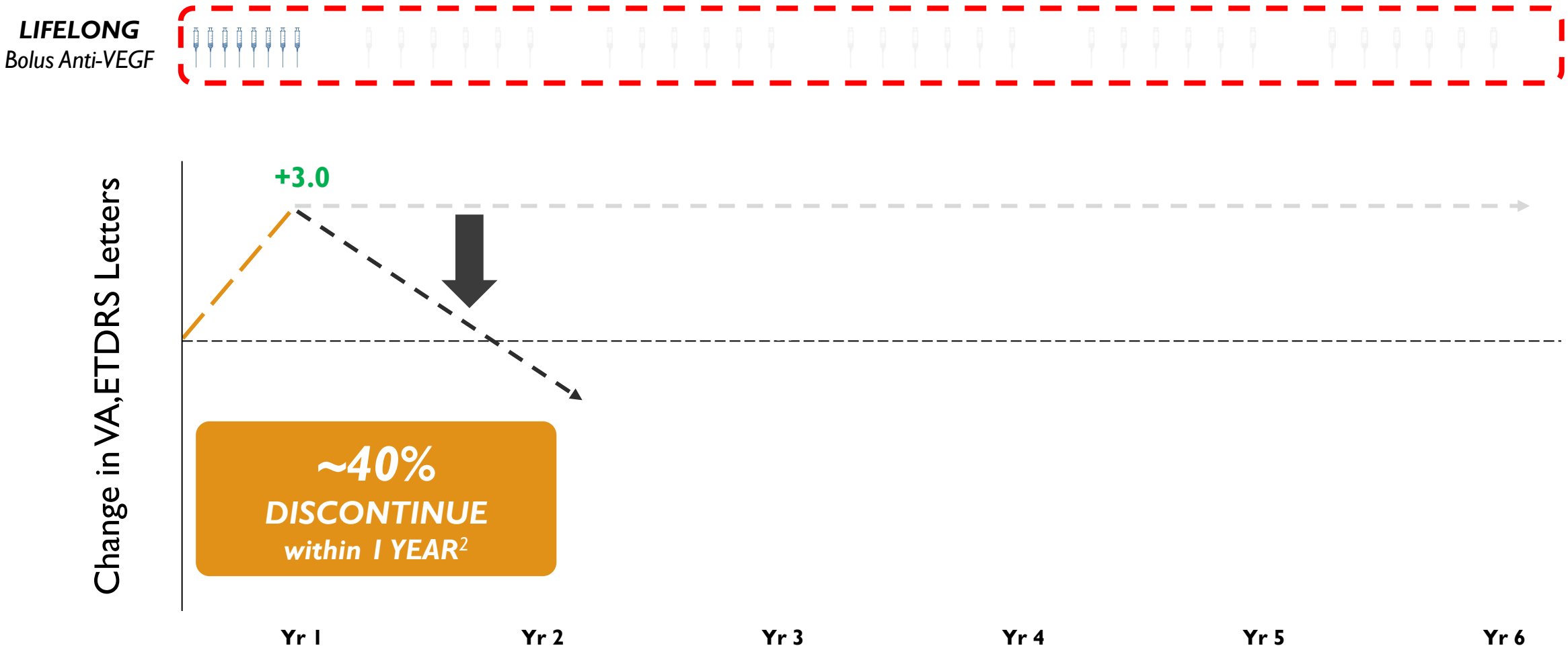
Prevalence sourced from Marketscope Retina Market Report 2023. Anti-VEGF market sourced from GlobalData, GrandView Research.

Lifelong Burdensome Bolus Anti-VEGF Injections Are Needed to Preserve Vision: ~30 Injections over 5 Years



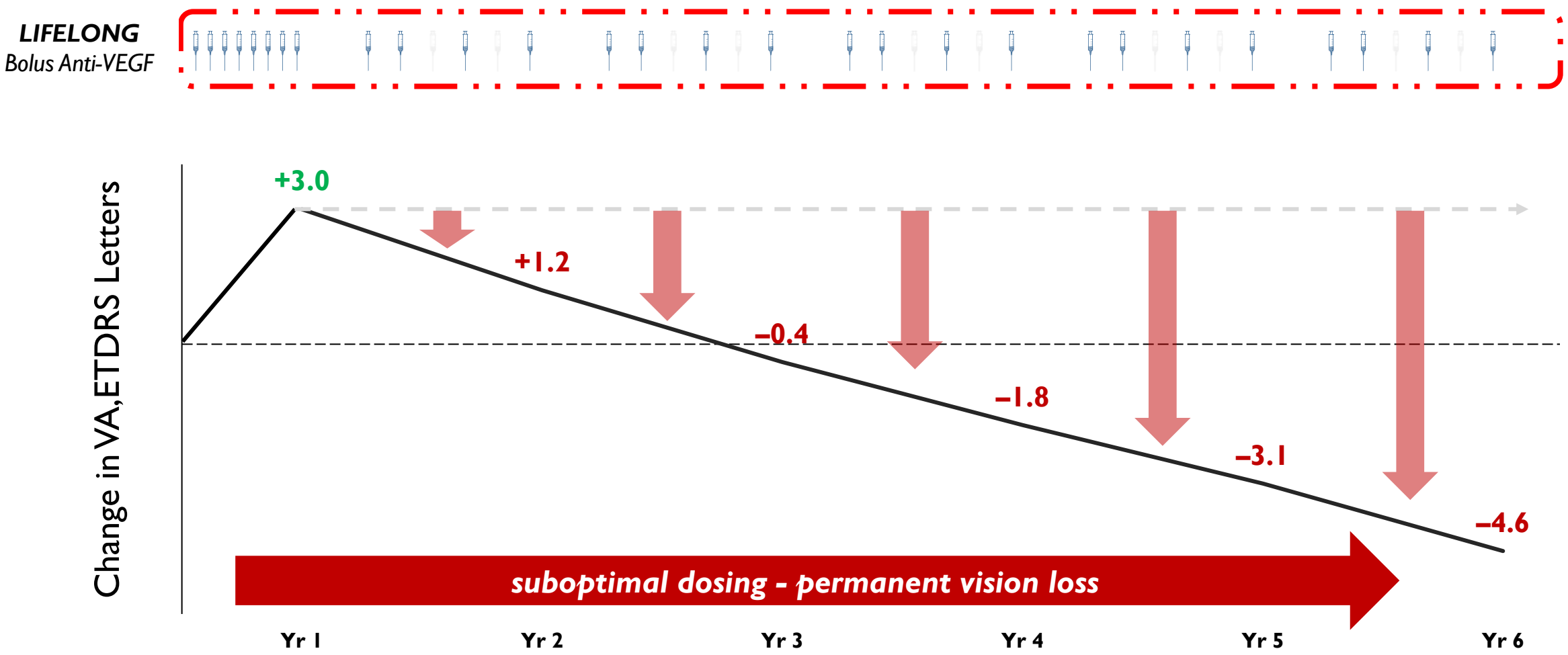
1. Holz FG, *et al. British Journal of Ophthal* 2015;99:220-226. More visits and injections appeared to be correlated with more successful maintenance of visual acuity gains, including in SEVEN-UP (Seven Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials),

In Real World, Treatment Discontinuation is Common: Current Bolus Treatment Regimens are NOT Sustainable



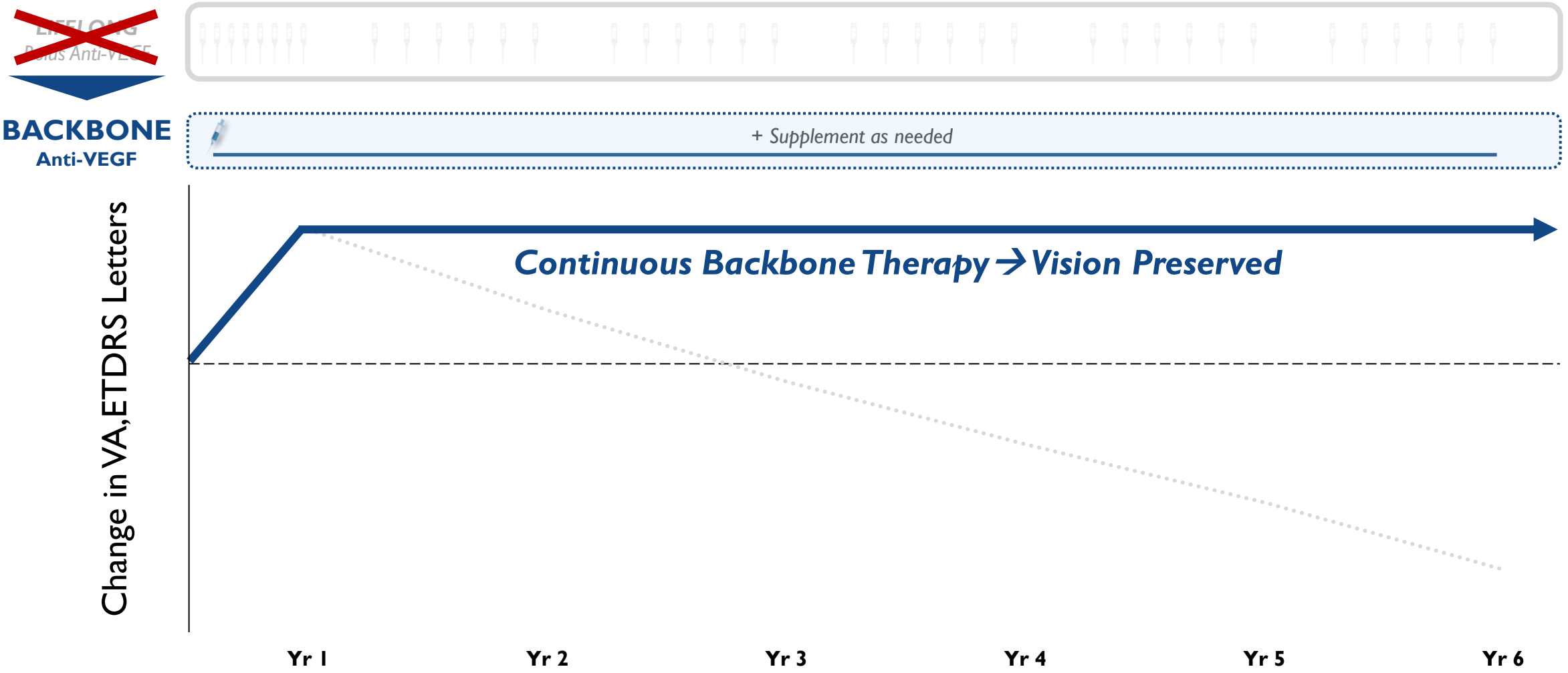
1. Wykoff et al.: *Ophthalmol Sci.* 2023 Oct 31;4(2):100421.; n=135,384 at Yr 1; 6,878 at Yr 6. 2. Khanani AM, et al. *Ophthalmol Retina.* 2020;4(2):122-133.

In Real World, Patients Remaining on Treatment: Inability to Maintain Burdensome Injection Regimen Leads to Unrelenting Vision Loss[1]



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

Solving the Unmet Need: Continuous Backbone Treatment to Control Disease & Protect Vision Without Lifelong Burdensome Injections

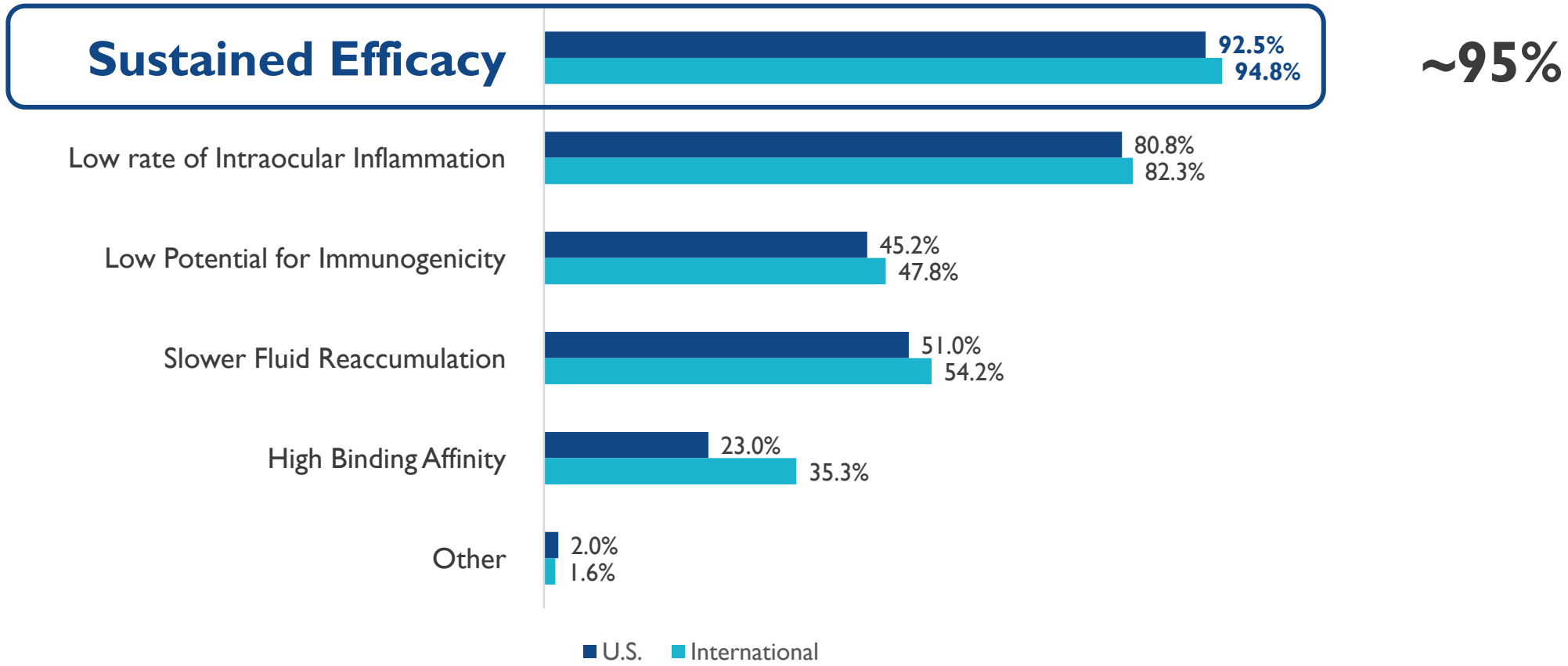


Wykoff et al.: Ophthalmol Sci. 2023 Oct 31;4(2):100421.; n=135,384 at Yr 1; 6,878 at Yr 6

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

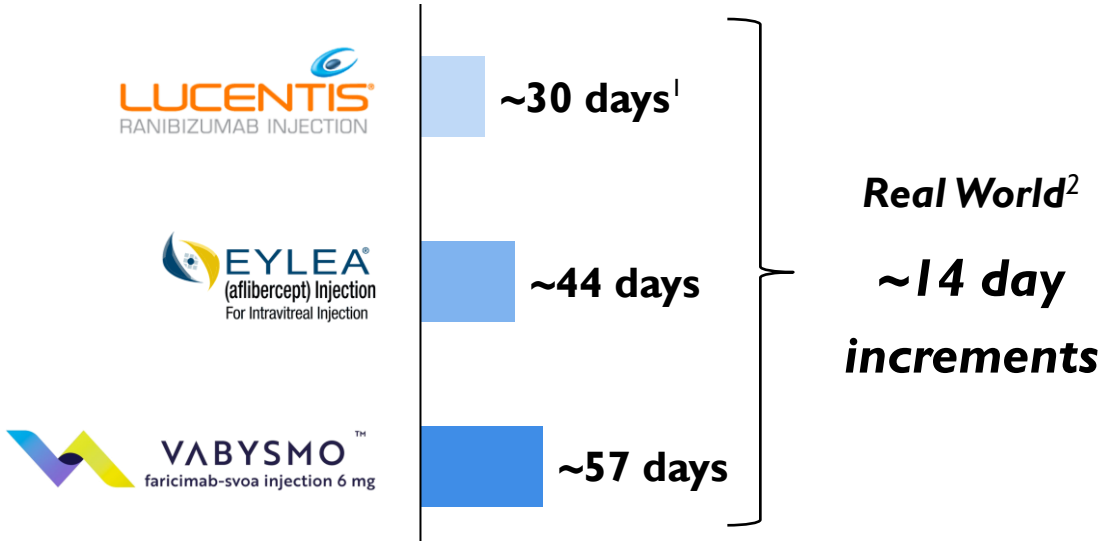
ASRS Preferences and Trends (PAT) Survey 2025

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

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



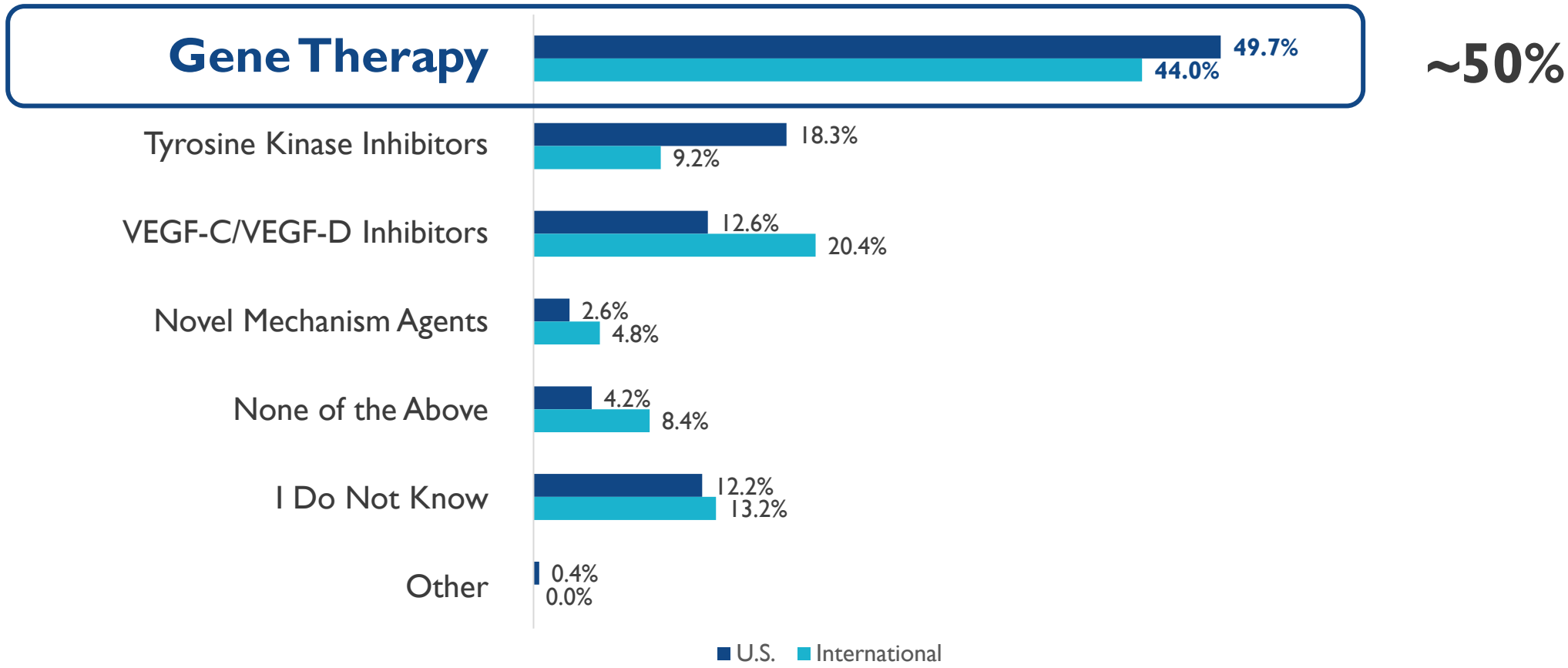
	Implied **Treatment Burden Reduction vs. Predecessor**	**Injection-free Potential**	**Net Sales Year 3 Post-Launch**
LUCENTIS RANIBIZUMAB INJECTION			**$1.8B**
EYLEA (aflibercept) Injection For Intravitreal Injection	↓ **~30%**	**0%**	**$3.3B**
VABYSMO™ faricimab-svoa injection 6 mg	↓ **~25%**		**$4.4B**

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.

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

ASRS Preferences and Trends (PAT) Survey 2025

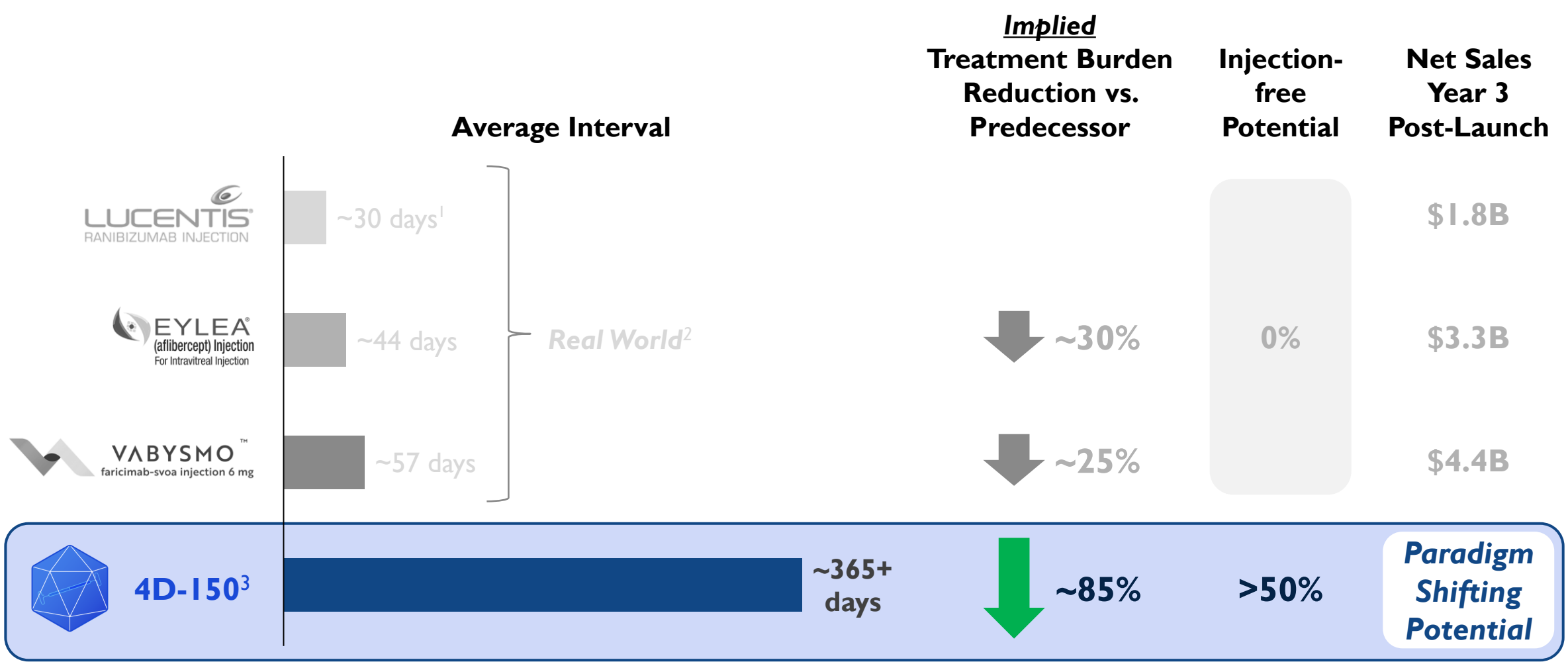
Which pipeline treatment for wet AMD **excites you most?**



~50%

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

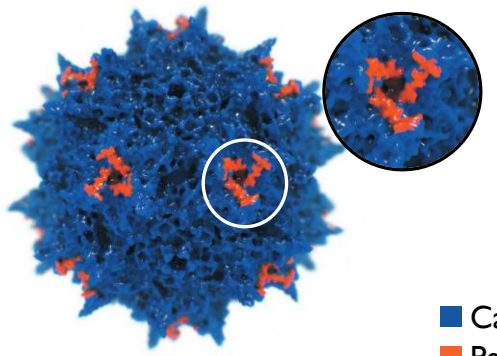
4D-150 Durability Profile would be Paradigm-Shifting



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.

4D-150 is Designed as Backbone Therapy to Provide Safe & Continuous Disease Control with Lifelong Anti-VEGF Expression Potential

R100 Capsid



- ✓ 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 studies[1]

4D-150 Backbone Therapy Target Profile

Single, in-office IVT Injection	Predictable prophylactic steroid eyedrop taper	Potential for lifelong durability[2]

*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-150 Wet AMD Development Program: Comprehensive Strategy Studying Increasingly Early-Stage Populations

PRISM Phase 1/2

	Phase 1/2a Safety, Proof of Concept	**Phase 2b** Clinical Activity in Broader Population	**Phase 2b Subgroup** Phase 3-Comparable	**4FRONT-1 / 4FRONT-2 Phase 3**
Phase 3 Dose 3E10 vg/eye (N=)*	**24**	**30**	**15**	**~480**
Population:	***Severe, Recalcitrant***	***Broad***	***Recently Diagnosed****	***Tx Naïve / Recently Diagnosed****
Mean Injections in Last 12 Mo.	10.2	4.4	2.7	0-4
Mean CST	425 µm	336 µm	304 µm	≤500 µm
Mean Time Since Dx	3.7 years	1.8 years	0.2 years	≤0.5 years

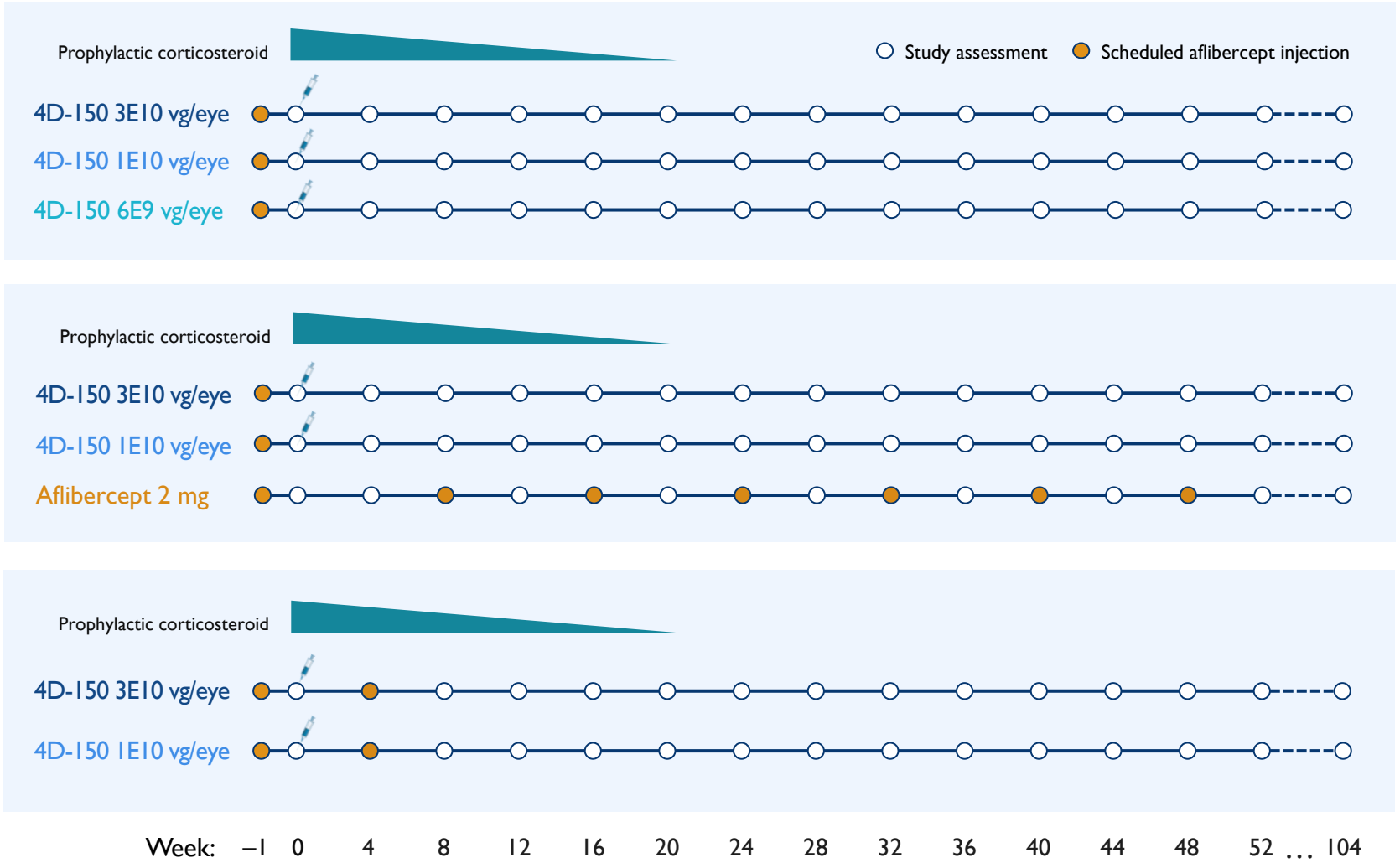
*Phase 3 dose. **≤0.5 years with previous treatment.

Wet AMD Phase 1/2 Schemas

Phase 1
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

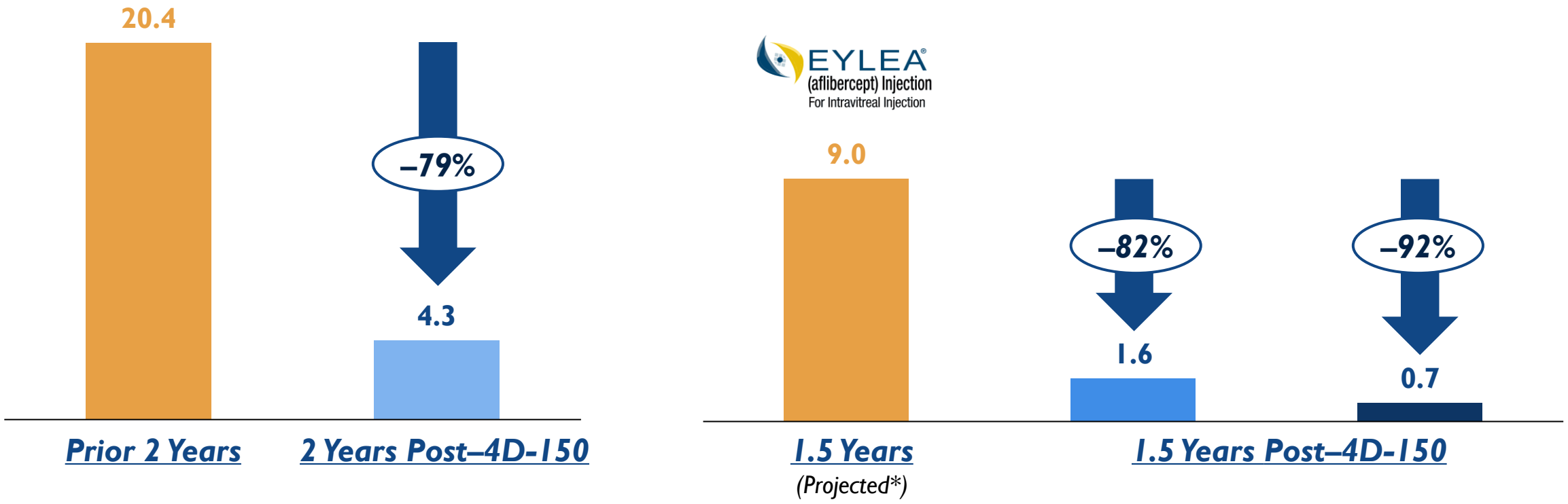
New vision-threatening hemorrhage due to wet AMD per investigator

*BCVA and CST.
CST, central subfield thickness; BCVA, best corrected visual acuity

4D-150 Demonstrated Transformative Treatment Burden Reduction Through 1.5 to 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*



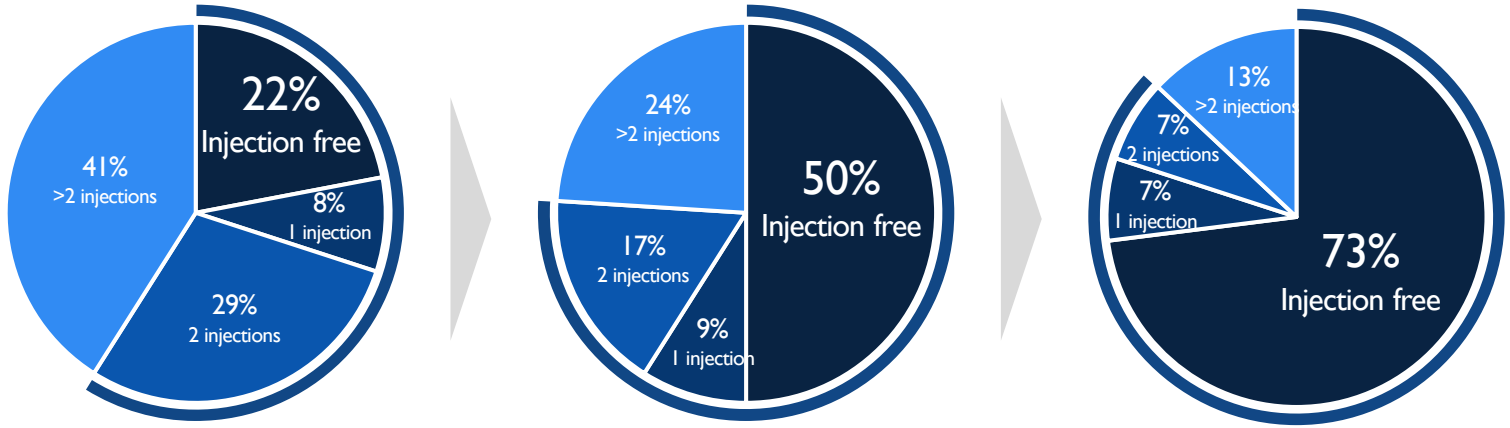
Data cutoff of August 22, 2025. *Projection based on last loading dose in Phase 2b and approved dosing schedule for aflibercept in wet AMD.

4D-150 Demonstrated Transformative Treatment Burden Reduction Through 1.5 to 2 Years in Multiple Wet AMD Patient Populations

PRISM Phase 1/2

Phase 3 Dose (3E10 vg/eye): Supplemental Anti-VEGF Injections Post–4D-150

Severe, Recalcitrant	*Broad*	*Recently Diagnosed*



59%	**76%**	**87%**
≤2 injections	≤2 injections	≤2 injections
over 2 years	***over 1.5 years***	***over 1.5 years***

4FRONT-1 / 4FRONT-2 Phase 3

Treatment Naïve & Recently Diagnosed

Topline 1-year data expected:

4FRONT-1 ***H1 2027***

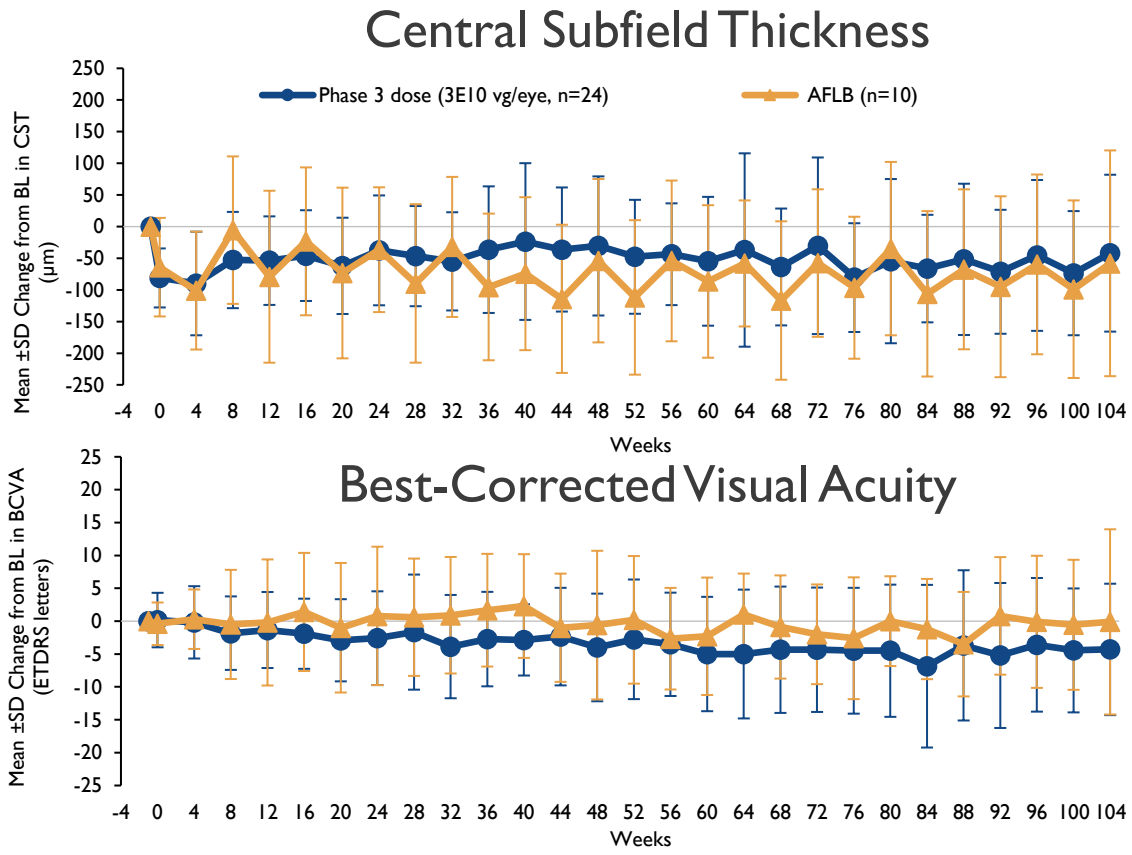
4FRONT-2 ***H2 2027***

Data cutoff of August 22, 2025.

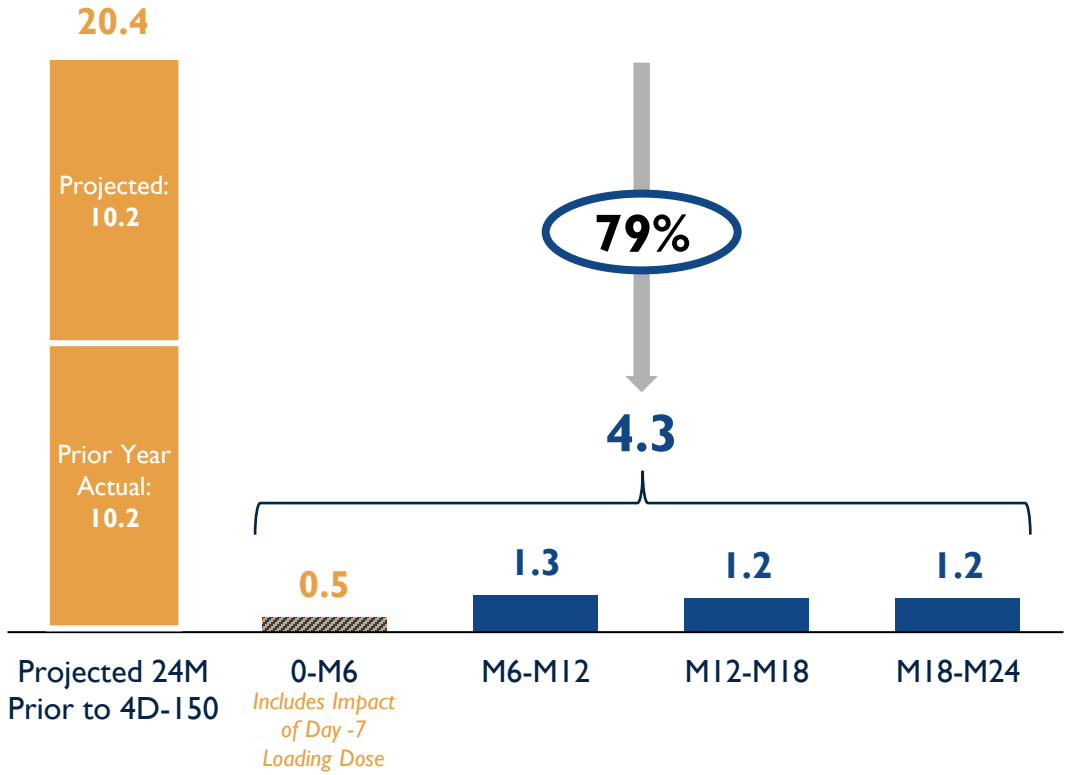
Results Through 2 Years Post–4D-150 in a Severe, Recalcitrant Population

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

Anatomy & Visual Acuity 4D-150 vs. Aflibercept



Treatment Burden Reduction Post–4D-150 (Phase 3 Dose): 6-month Segments

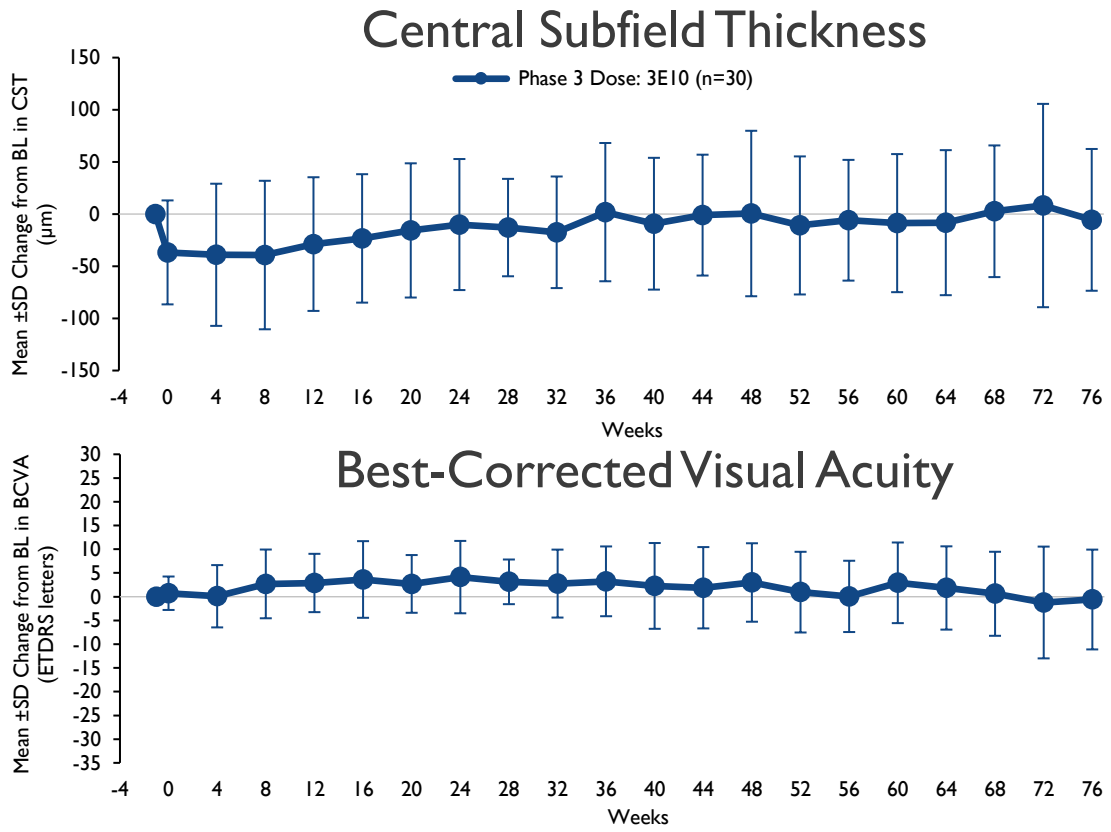


Data cutoff of August 22, 2025.
CST, central subfield thickness; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; AFLB, aflibercept.

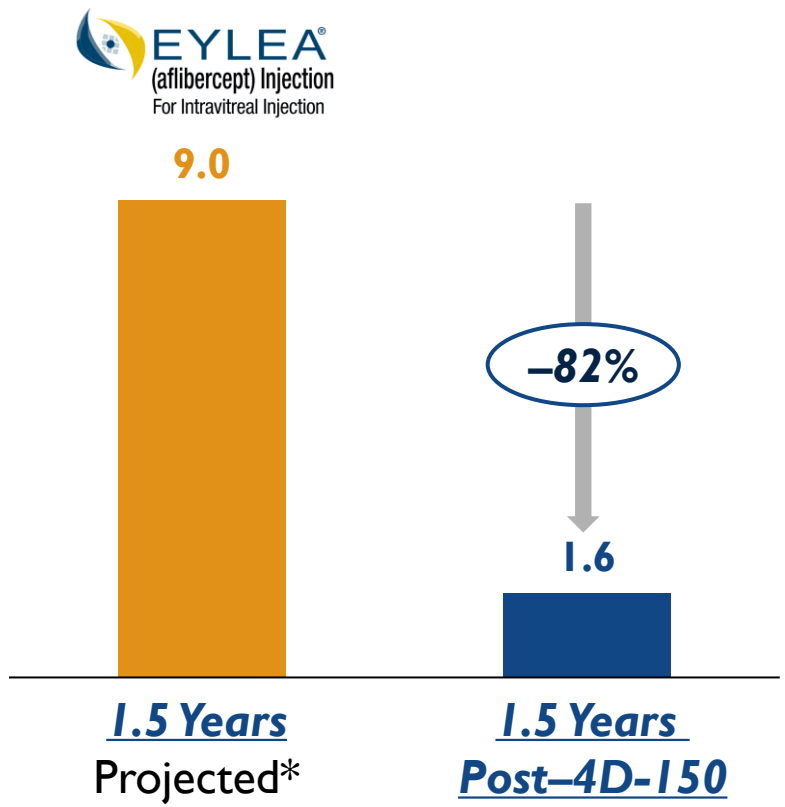
Results Through 1.5 Years Post–4D-150 in a Broad Population

Visual Acuity & Anatomy Stable With Robust Reduction in Treatment Burden

Anatomy & Visual Acuity Post–4D-150



Treatment Burden Post–4D-150

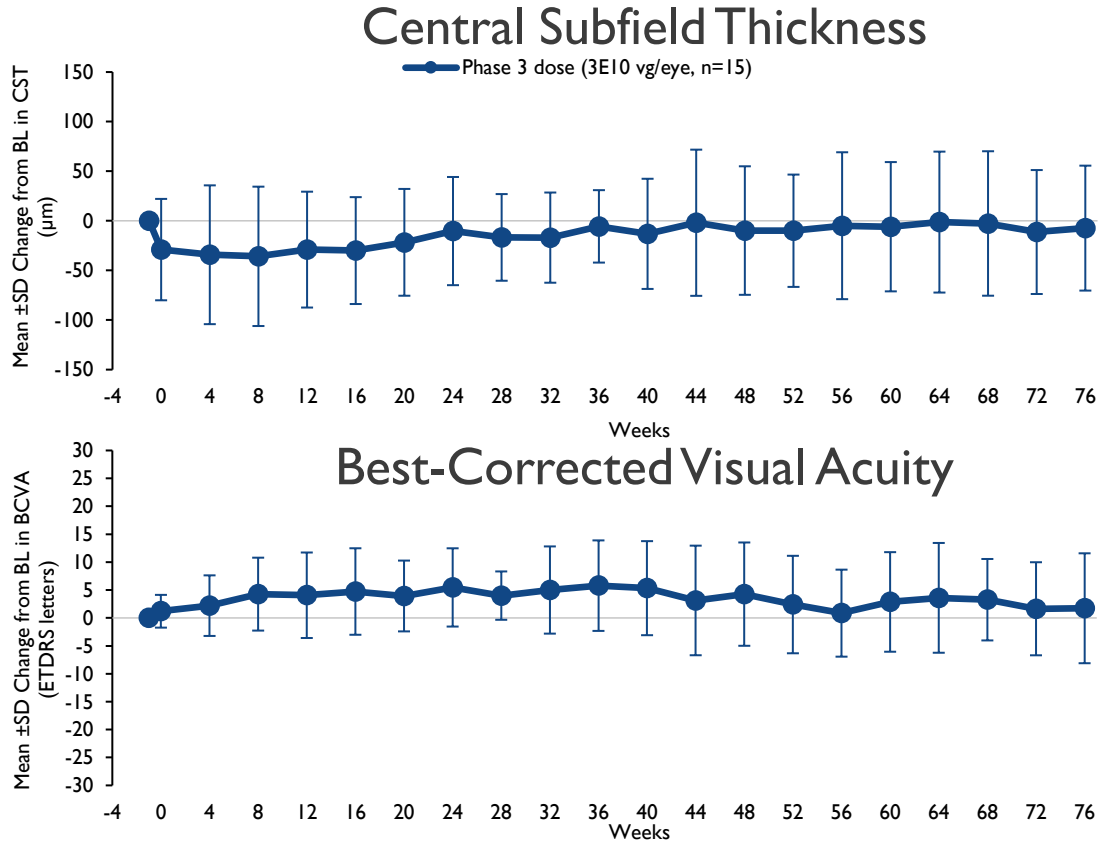


Data cutoff of August 22, 2025.
CST, central subfield thickness; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study. *Projection based on last loading dose in Phase 2b and approved dosing schedule for aflibercept in wet AMD.

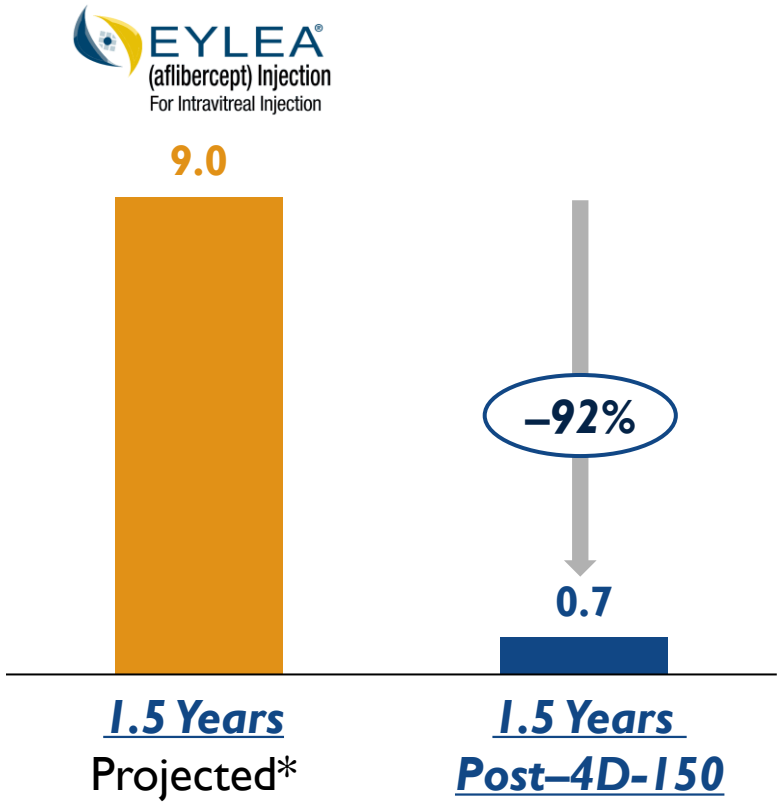
Results Through 1.5 Years Post–4D-150 in Recently Diagnosed Population

Visual Acuity & Anatomy Stable With Robust Reduction in Treatment Burden

Anatomy & Visual Acuity Post–4D-150



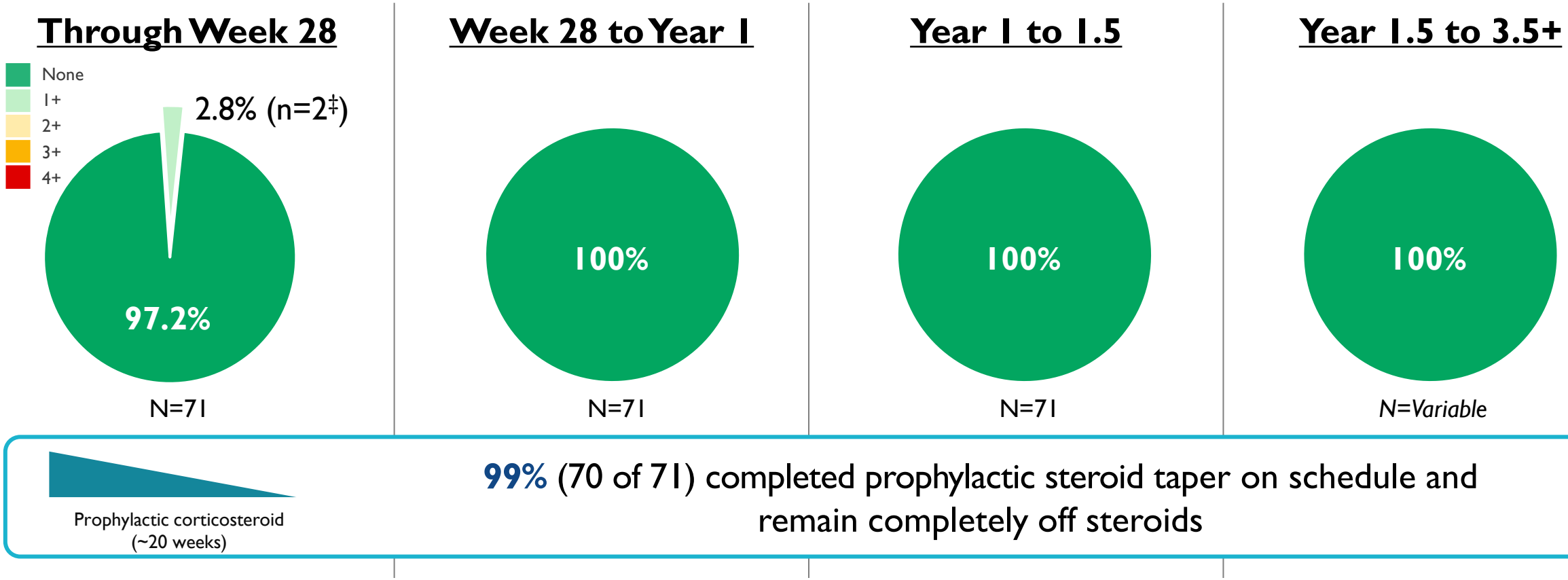
Treatment Burden Post–4D-150



Data cutoff of August 22, 2025.
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)



Data cutoff of August 22, 2025.
†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-150 vs. aflibercept 2mg (Q8W) after 3 loading doses

4FRONT-1

North America

N=480

100% Treatment naïve

✓ **Enrollment completed**

4FRONT-2

Global

N=480

60% Treatment naïve

*Up to 40% Previously treated**

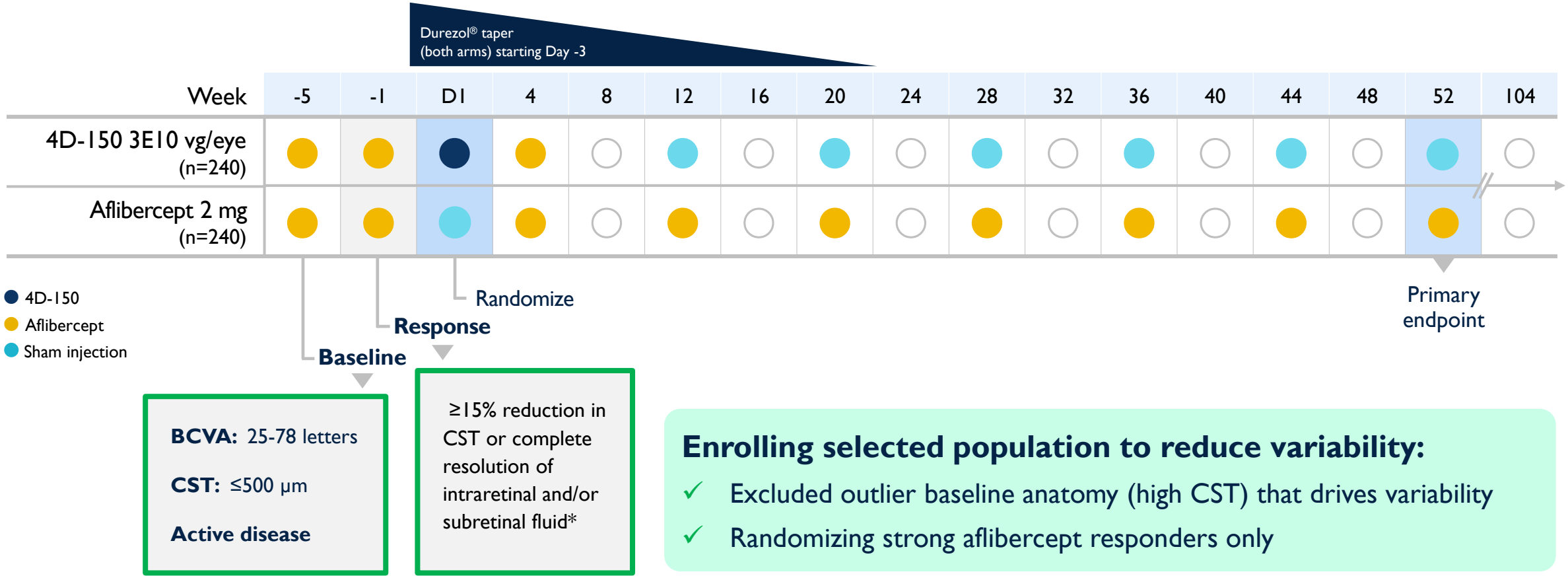
Enrolling

- ✓ **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



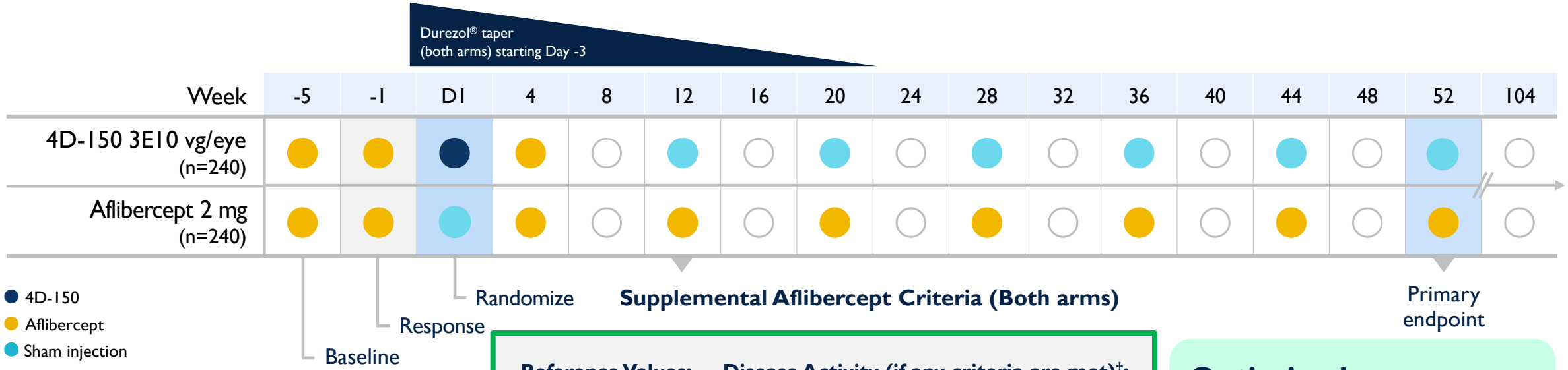
Enrolling selected population to reduce variability:

- ✓ Excluded outlier baseline anatomy (high CST) that drives variability
- ✓ Randomizing strong aflibercept responders only

*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



Reference Values:

BCVA: **Average of Week 4 & 8**

CST: **Week 8**

Disease Activity (if any criteria are met)†:

Vision & Anatomy: ≥5 letter loss in BCVA AND ≥50 µm increase in CST

Vision: ≥10 letter loss in BCVA

Anatomy: ≥100 µm increase in CST

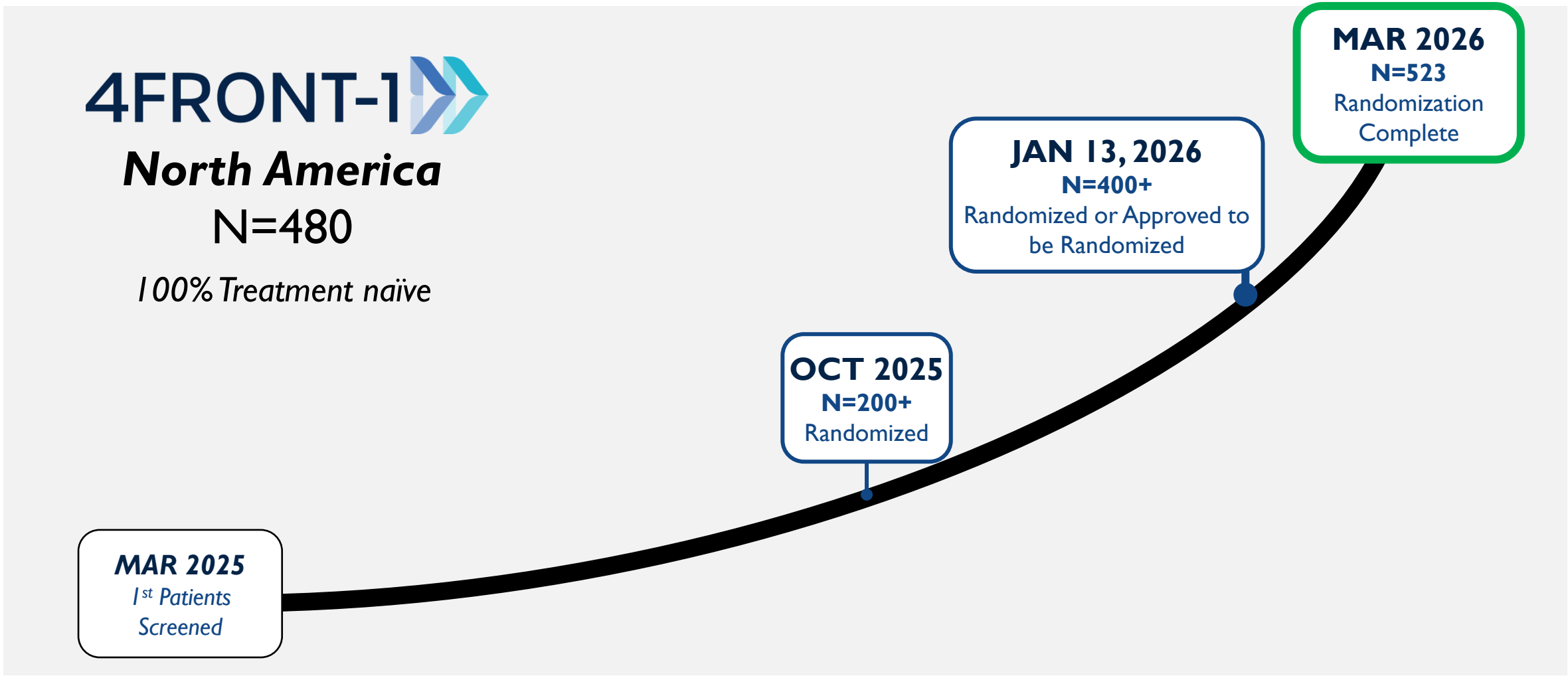
New vision-threatening hemorrhage

Optimized Supplemental Criteria

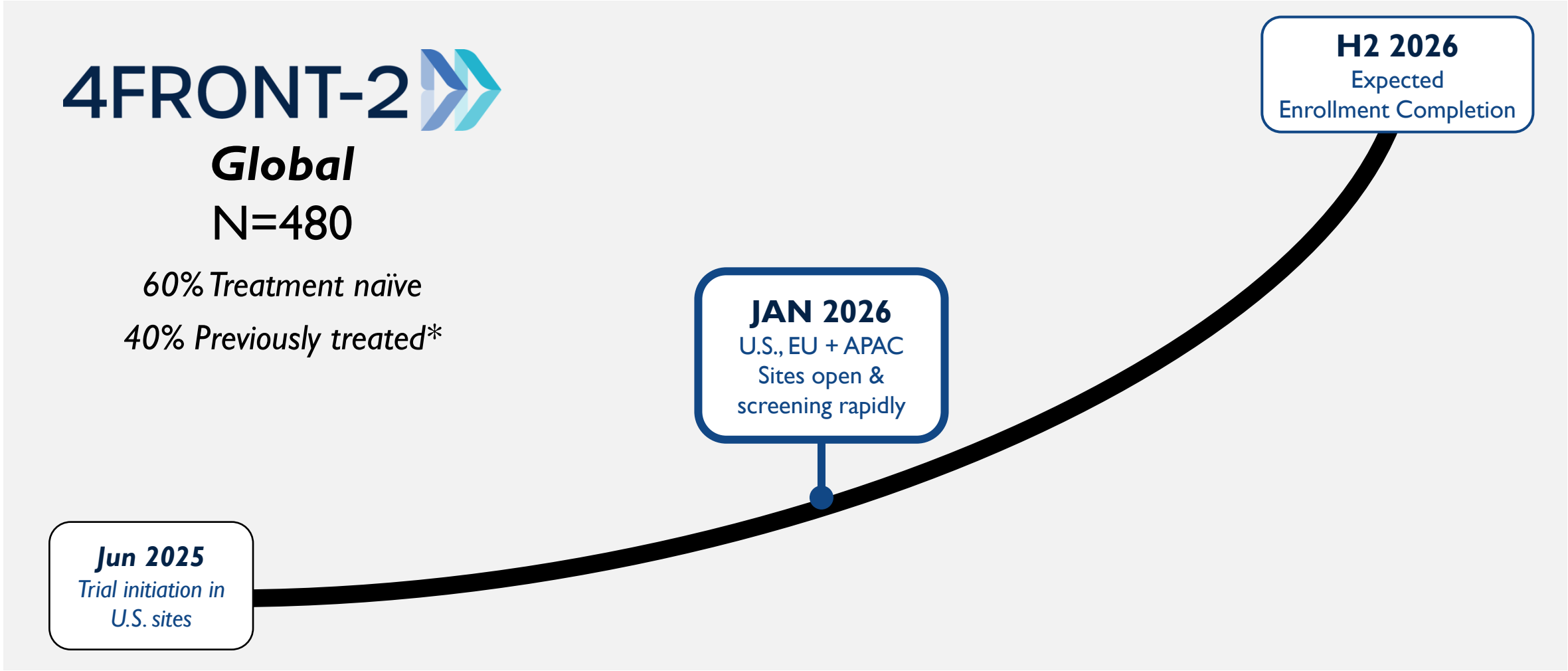
- ✓ Protects BCVA
- ✓ Clinically relevant treatment burden reduction result

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

4FRONT-1 Enrollment Completed, Significantly Exceeding Initial Expectations while in a Treatment-Naïve Population



4FRONT-2 Rapidly Executing & Enrolling Globally: U.S., EU & Japan Open



*1-4 prior injections, diagnosed within 6 months.

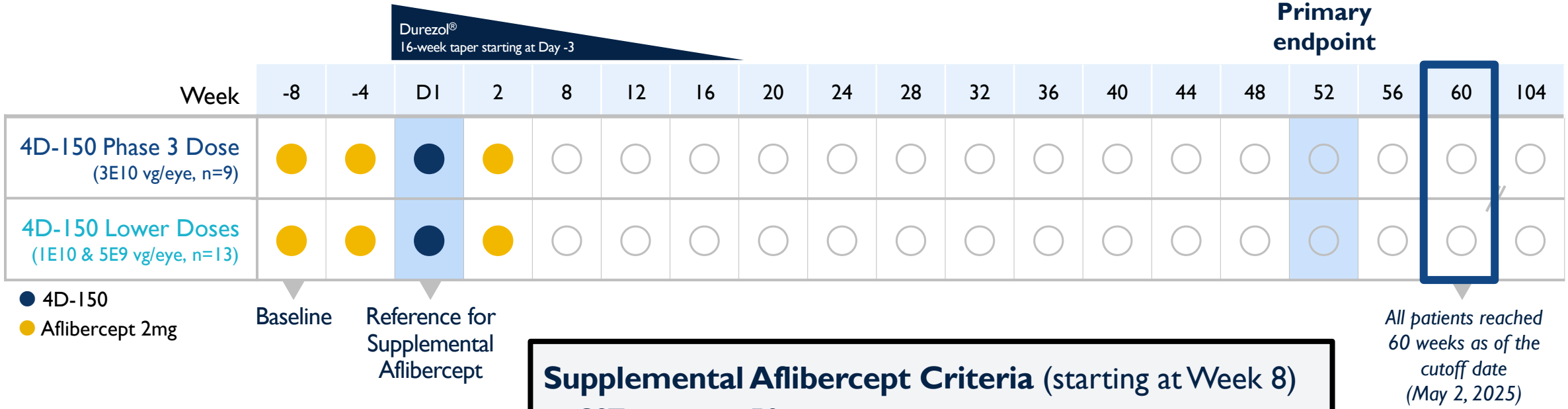
SPECTRA Enrolled DME Patients with Focus on Safety & Dose Selection

Key Eligibility Criteria

Diagnosis within 2 years, CST ≥350 µm (includes treatment naïve)

Confirmed anti-VEGF response (CST decrease ≥40 µm at Week –1 versus Week –8)

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



Supplemental Aflibercept Criteria (starting at Week 8)

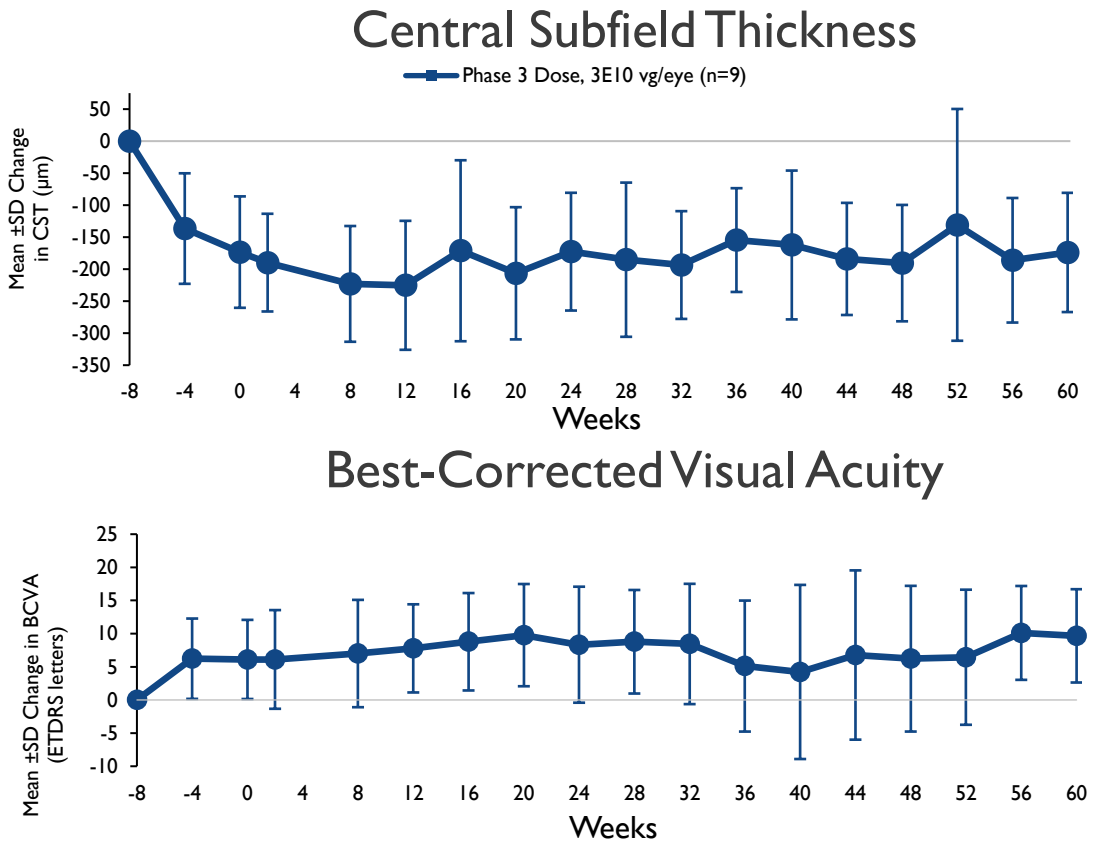
- CST increase ≥**50 µm**
  - ***Injections continue*** until change in CST is ≤30 µm on 2 consecutive visits ***or*** CST is ≤325 µm

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.

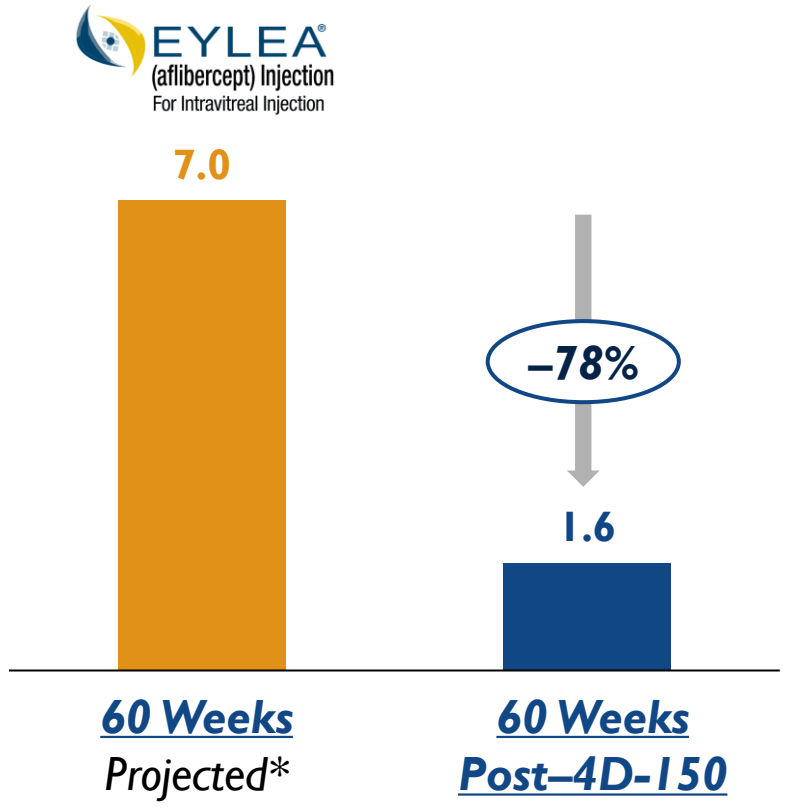
Results Through 60-weeks Post–4D-150 in DME

Visual Acuity & Anatomy Stable With Robust Reduction in Treatment Burden

Anatomy & Visual Acuity 4D-150



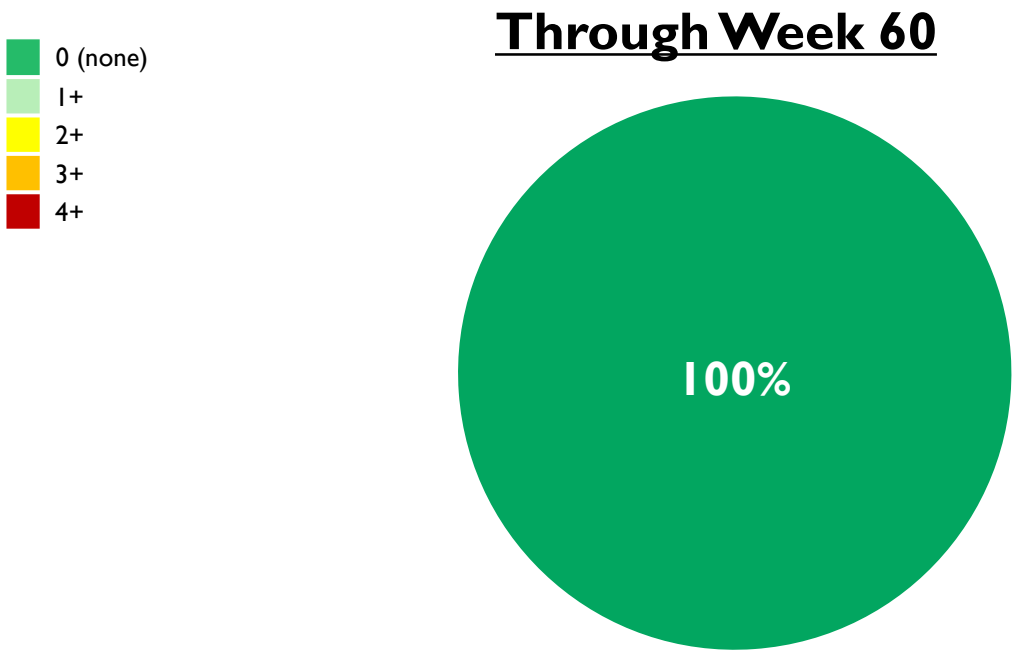
Treatment Burden Post–4D-150



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-150 Phase 3 Dose, 3E10 vg/eye (N=9)



Prophylactic corticosteroid
(~16 weeks)

100% (9 of 9) completed on schedule and remain completely off

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-150 in Asia-Pacific Region

4DMT Otsuka

4D-150 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-150 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
- **Q3 2026**: PRISM Phase 2b 2-year data
- **H2 2026**: 4FRONT-2 Phase 3 enrollment complete
- **H1 2027**: 4FRONT-1 Phase 3 topline data
- **H2 2027**: 4FRONT-2 Phase 3 topline data

Diabetic Macular Edema

- **Mid-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.

4DMT

4D-710

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

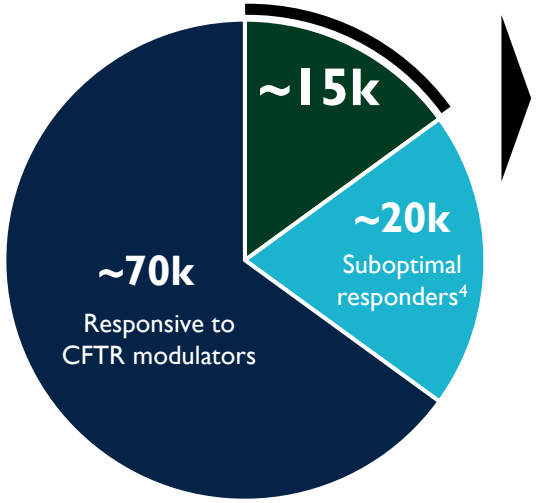
Cystic Fibrosis Lung Disease: High Unmet Need Despite Modulators

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 years[1]

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***

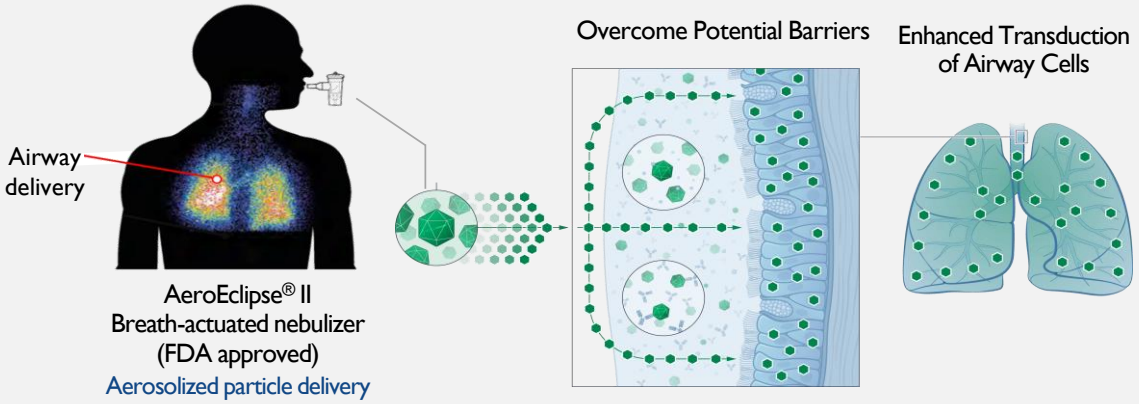
CFTR Modulator Market Size

~$11 Billion (2024)[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 2024 financial results.

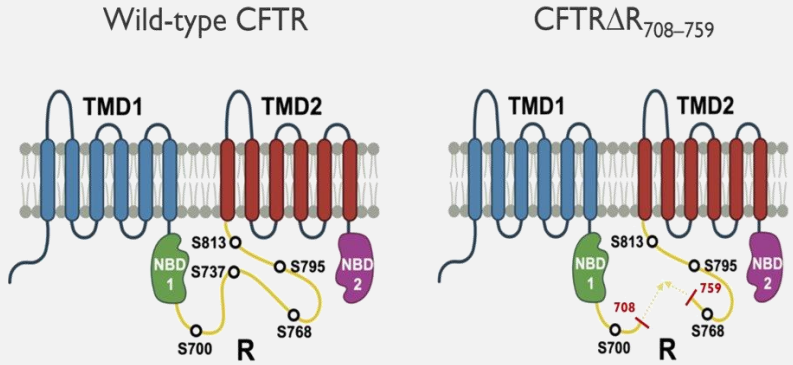
4D-710 Design: Durable, Redosable, Variant-agnostic Disease-modifying Therapy for CF Lung Disease

Novel AAV Vector: A101



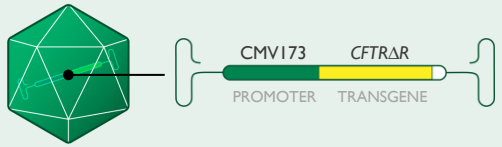
- ✓ Mucus penetrant
- ✓ Transduction of multiple airway cell types
- ✓ Resistance to pre-existing immunity

Payload: *CFTRΔR* Transgene



- Partial deletion in the regulatory domain
- **Normal channel structure, function and regulation**[1,2]
- Corrected disease phenotypes in CF pig model[3]

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

Focus of Phase 1:
Dose Finding

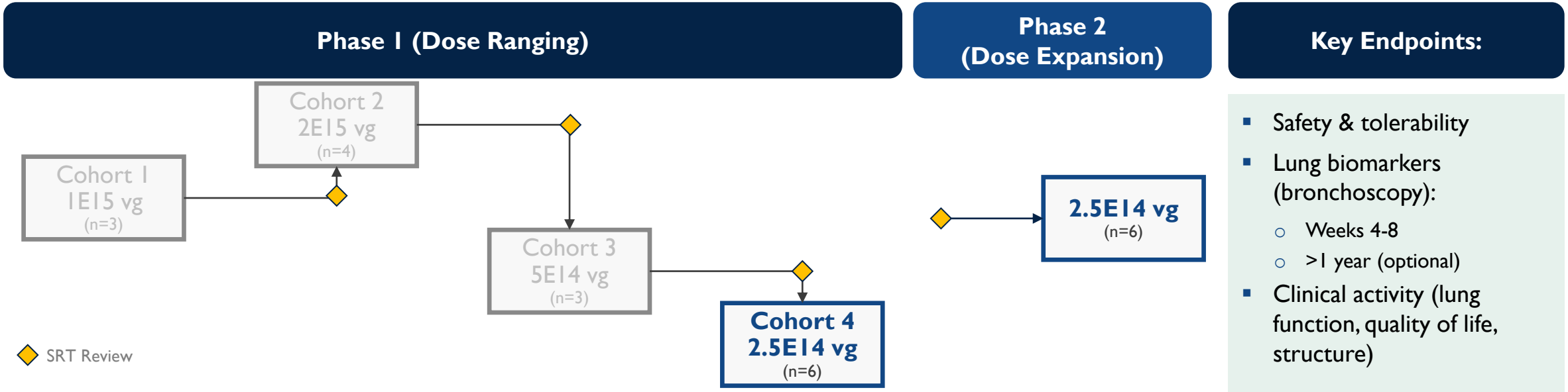
- **Safety** ✓
- **Physiologically relevant**
  CFTR expression levels
  (ISH, IHC) ✓
- **Clinical activity**
  ($ppFEV_1$, $LCI_{2.5}$, CFQR-R-R) ✓

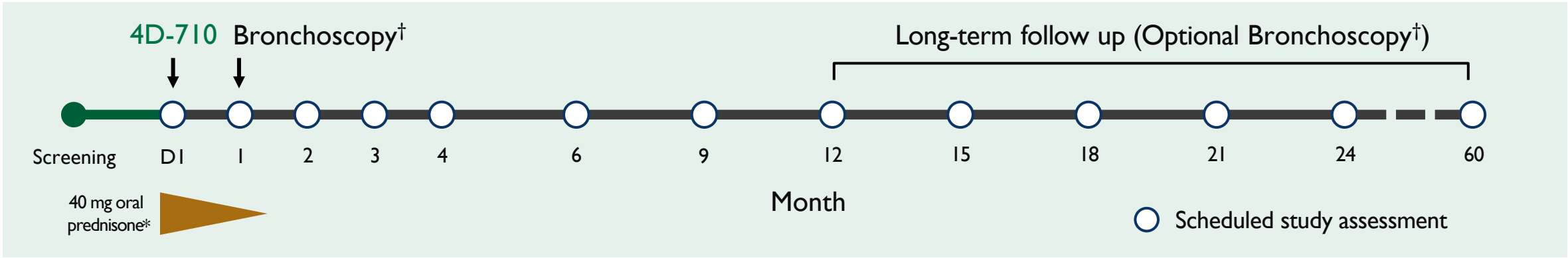
Phase 2 Dose: 2.5E14 vg

Focus of Phase 2 (Enrolling):
Characterize Clinical Activity

- *Stability or improvement in* ***large-/mid- airway disease*** *($ppFEV_1$)*
- *Improvement in* ***small airway disease*** *($LCI_{2.5}$)*
- *Improvements in* ***respiratory symptoms*** *(CFQ-R-R)*
- *Exploratory: evidence of* ***decreased mucus burden*** *(HRCT)*

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). $ppFEV_1$, 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); FEV$_1$, 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

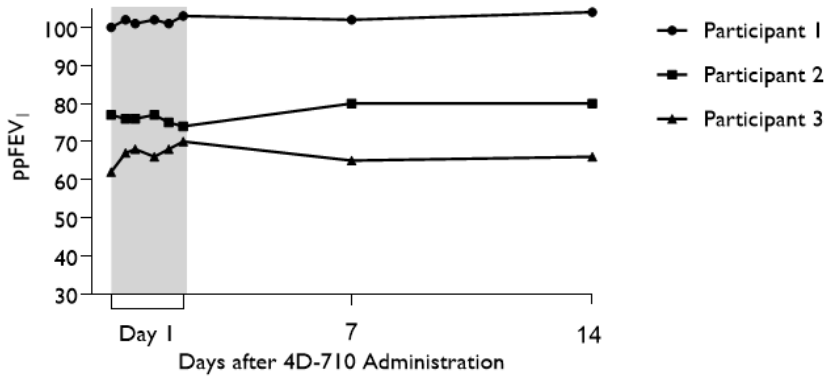
1. Routine ACT (Historical)
2. Baseline Spirometry

Bronchodilator: Albuterol

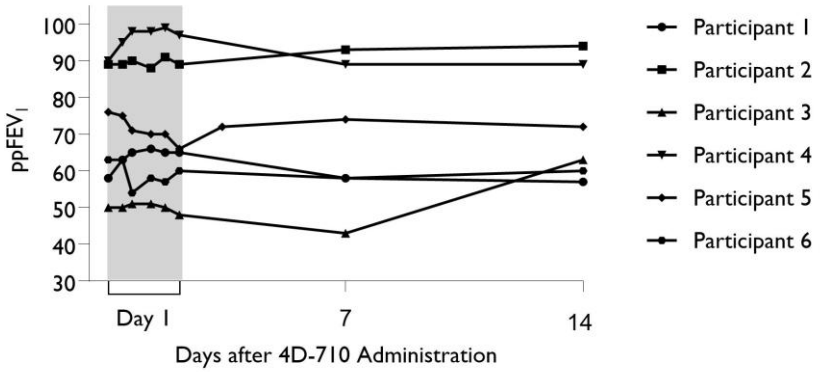
3. Repeat Spirometry
4. **4D-710** Nebulization
5. Spirometry During Dosing
6. Spirometry Post-Dosing

$ppFEV_1$

5E14 vg
Admin. Time
~90 Mins



2.5E14 vg
Admin. Time
~45 Mins

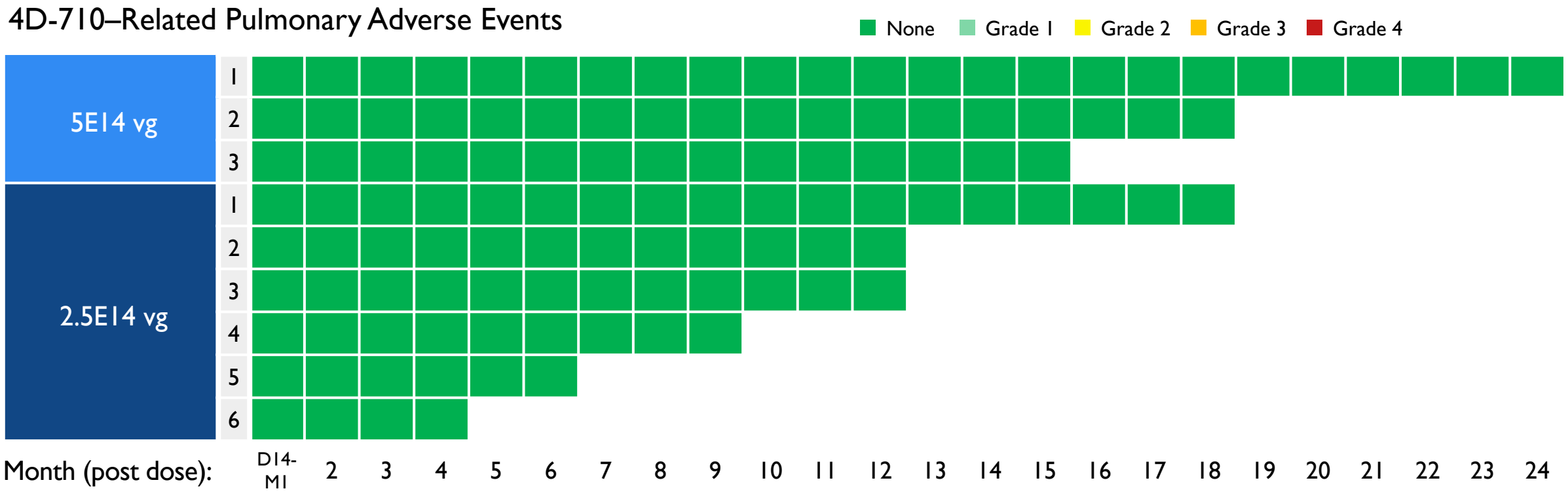


4D-710–Related AE

- Participant 1: **throat irritation** after dosing (Grade 1, ~5 sec), increased **productive cough** (Grade 1, Day 4-13)
- Participant 5: increased **cough and lightheadedness** during dosing (Grade 1, resolved Day 1 without intervention), **chest tightness and decrease in FEV_1** (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

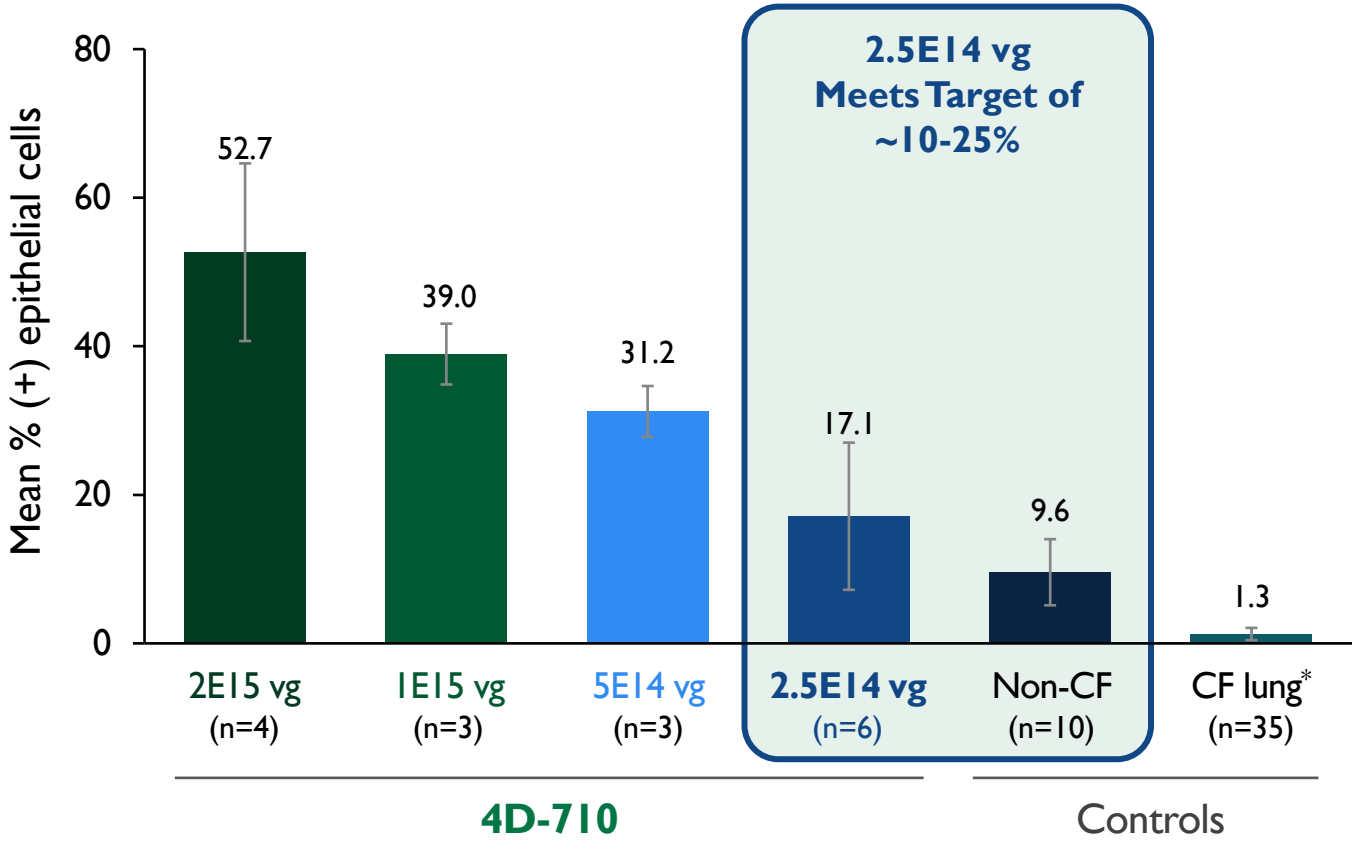


- Higher dose cohorts (1E15 & 2E15 vg): NO new related AEs since last update (up to 3.5 years of follow up)
- Non-Pulmonary 4D-710–Related AEs:
  - 5E14 vg (Participant 3): 1) Mental Fogginess: Grade 2, started Day 24 and resolved Day 35; 2) Stuttering: Grade 2, started Day 25 and resolved Day 35
  - 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

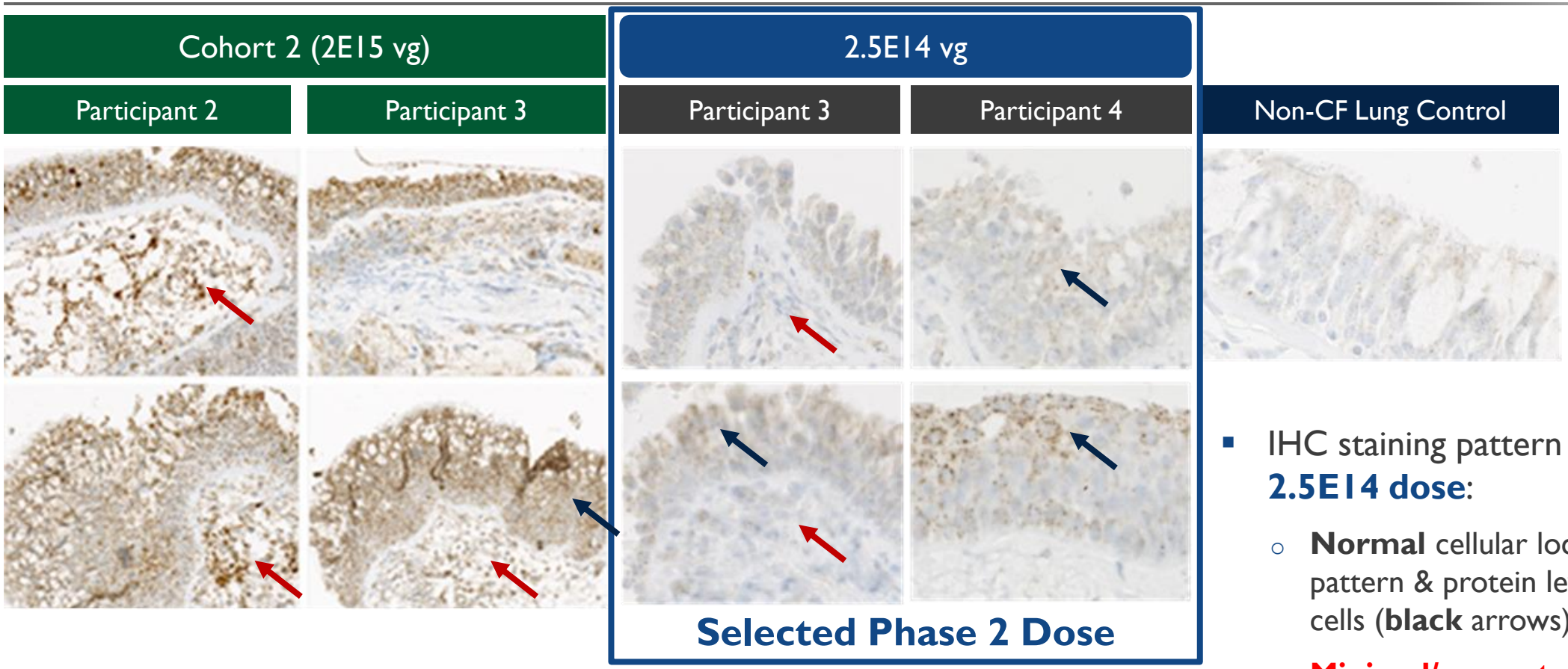


- Dose-dependent *CFTRΔR* mRNA expression in airway cells
- **2.5E14 vg dose (Cohort 4) meets target expression profile**[1,2]

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 ΔF508 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.

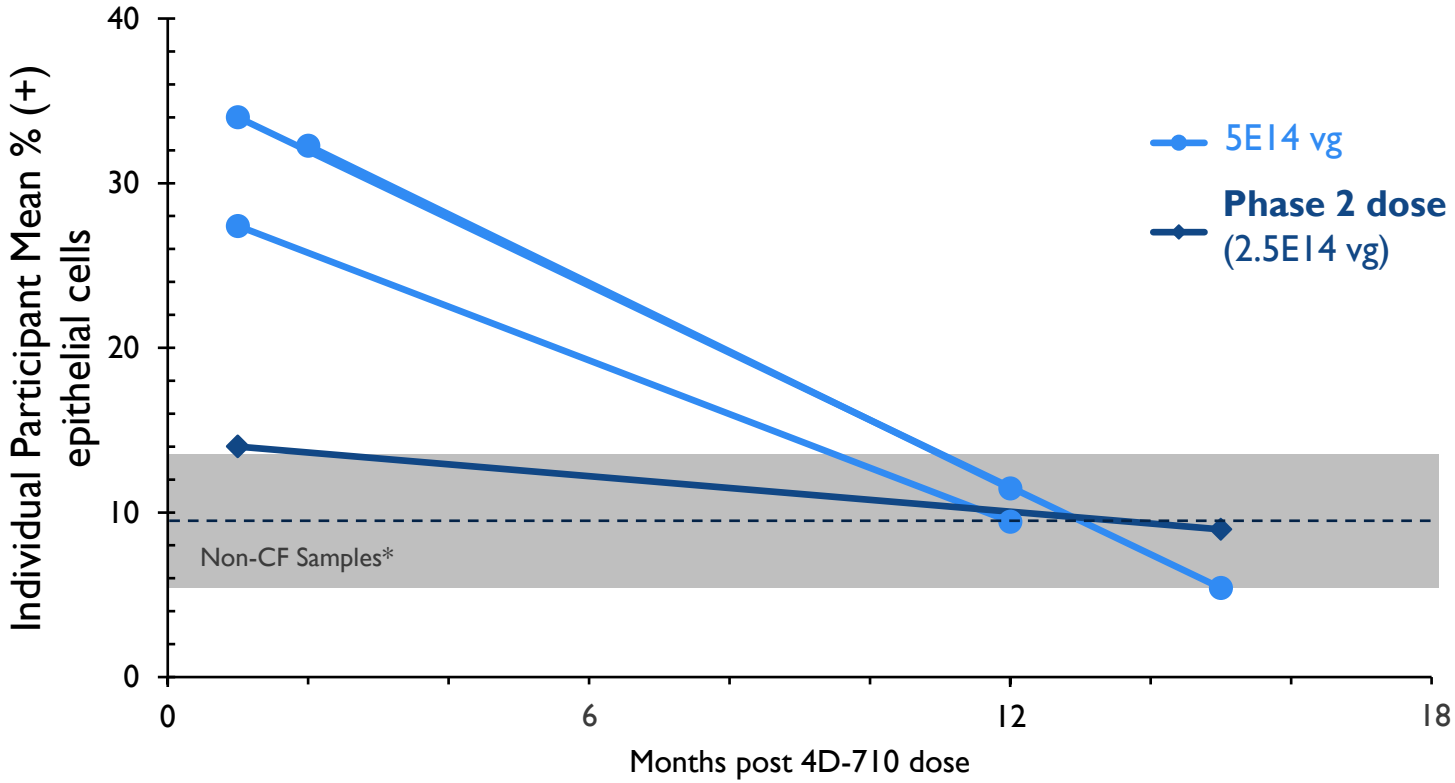
CFTR Protein Expression Meets Target Expression Pattern in Airway & Interstitial Areas at 2.5E14 vg Dose (Cohort 4)



- 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 *CFTRΔR* 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

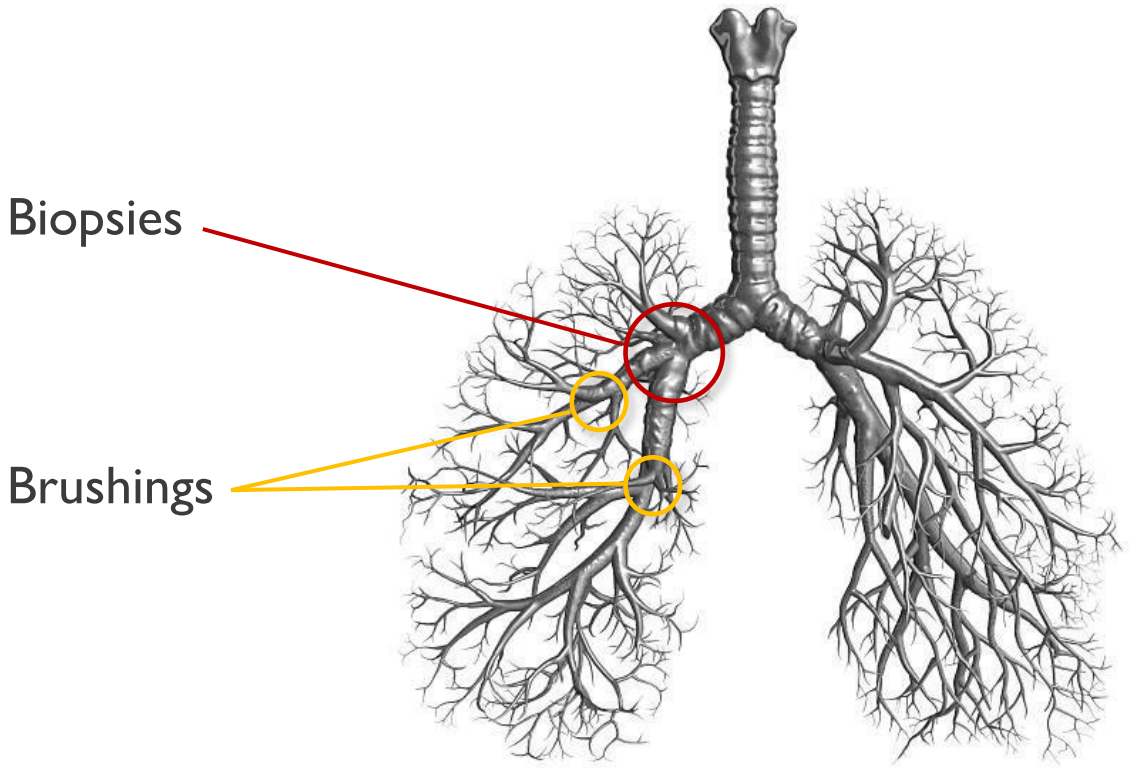
Next Steps

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 (±SD) in non-CF samples = 9.6% (±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 1 Trial

Lung Tissue Biomarkers



Pulmonary Clinical Activity Endpoints

Larger Airways

- $ppFEV_1$

Small Airways

- Lung Clearance Index ($LCI_{2.5}$)

New in Lower Dose Cohorts

Pulmonary Symptoms

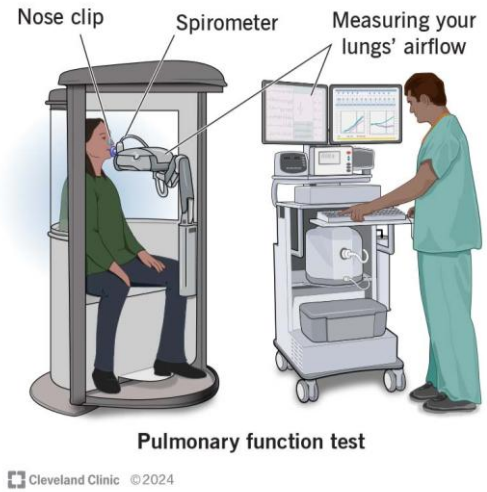
- CFQ-R-R

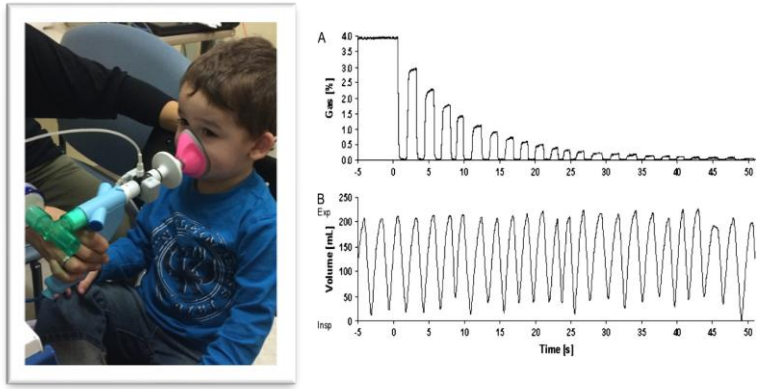
Structural/Functional Changes

- HRCT (analyses pending)

$ppFEV_1$, 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.

$ppFEV_1$ & $LCI_{2.5}$: Complementary Measures of Lung Function

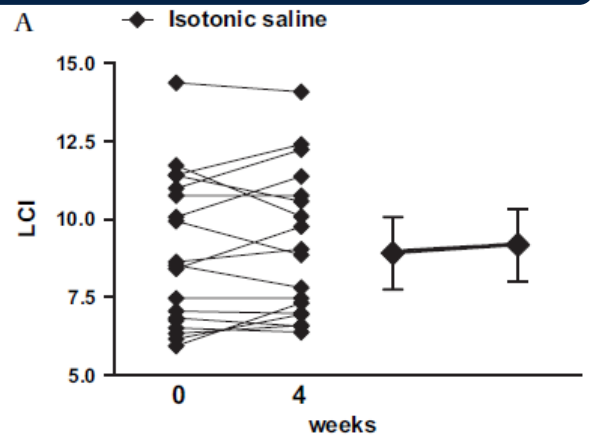




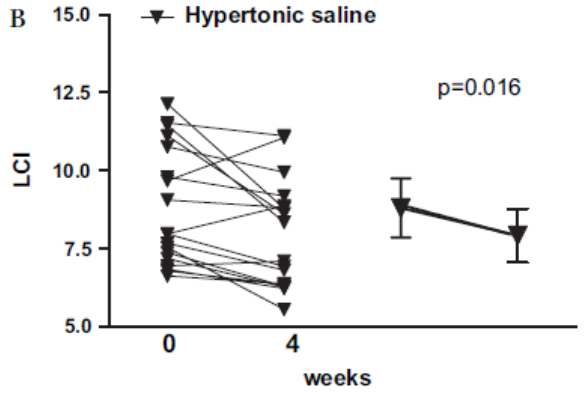
Measure / Endpoint	Spirometry: $ppFEV_1$	Multiple Breath Washout: $LCI_{2.5}$
Measures	*Lung restriction/obstruction, marker of **larger airway disease***	*Ventilation inhomogeneity, marker of **small airway disease***
Effort Dependent	**Yes**	**No**
Sensitivity to Early Disease	**Low**	**High**
Responsiveness to Intervention	**Medium** *may miss subtle improvement in early/mild disease*	**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 $ppFEV_1$ 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;

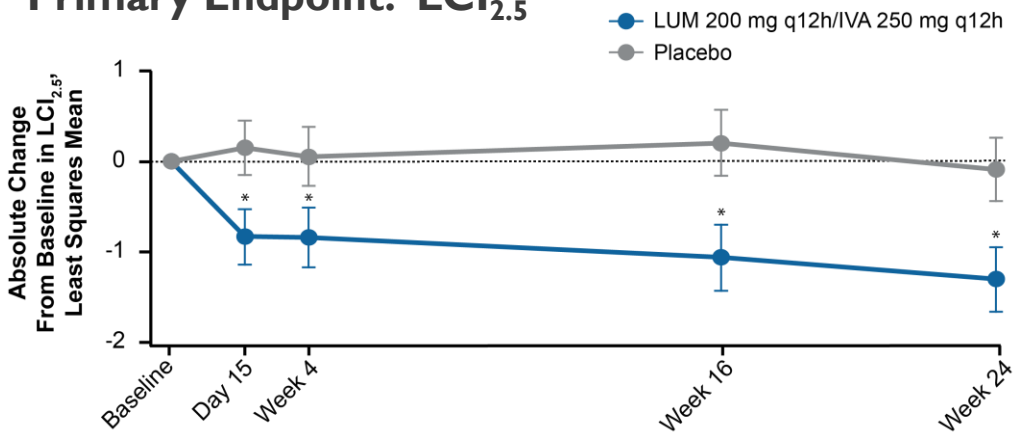
Outcome Analysis	HS vs. IS Treatment Effect*	Required Sample Size†
Spirometry:		
$ppFEV_1$	**1.8 ± 12.0**	**351**
$ppFEF_{25-75}$	5.3 ± 22.3	141
CFQ-R Questionnaire:		
Respiratory Domain	5.2 ± 14.2	61
Multiple-Breath Washout		
$LCI_{2.5}$	**1.16 ± 0.94 (p=0.016)**	**≤19**

$LCI_{2.5}$ 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.

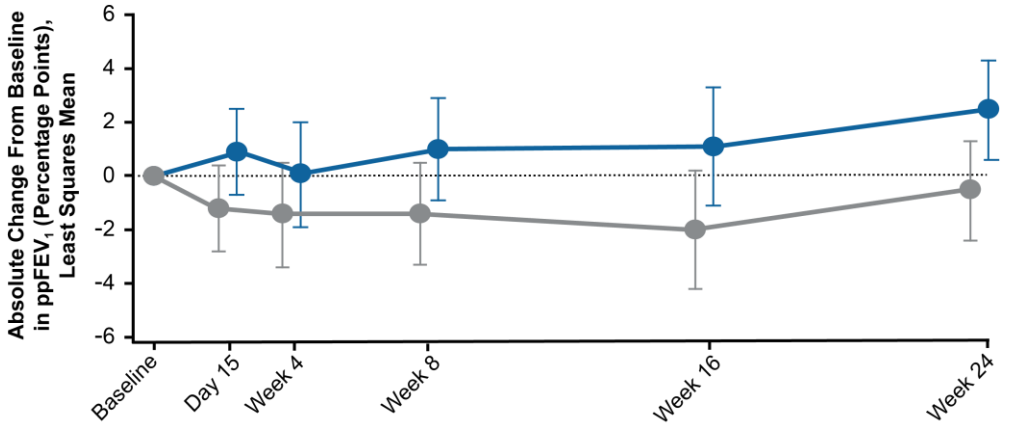
In Orkambi® Trial in Children, $LCI_{2.5}$ Demonstrated Robust Treatment Response at Every Timepoint vs. Placebo in Contrast to $ppFEV_1$

Primary Endpoint: $LCI_{2.5}$



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)** ***P*<0.0001**

Secondary Endpoint: $ppFEV_1$



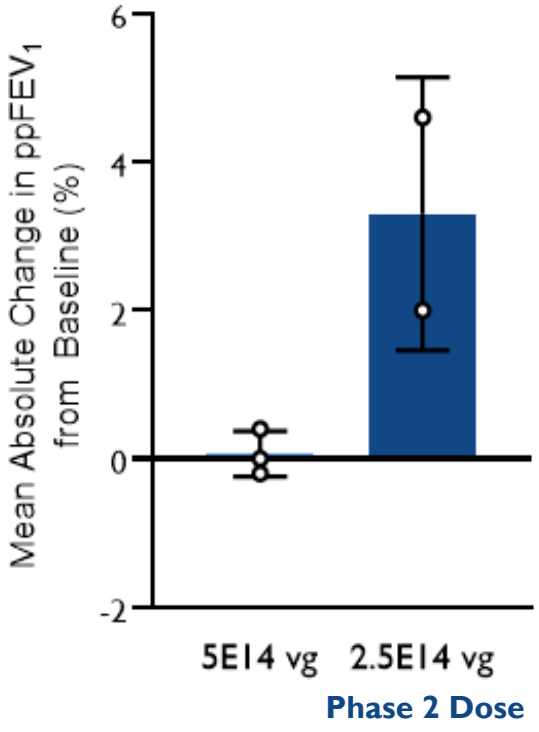
Endpoint	Placebo (n=101)	LUM/IVA (n=103)	Treatment Difference vs Placebo
Absolute change in $ppFEV_1$ through week 24	-1.3 (-2.8 to 0.2)	1.1 (-0.4 to 2.6)	**2.4 (0.4 to 4.4)** ***P*=0.0182**

*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.

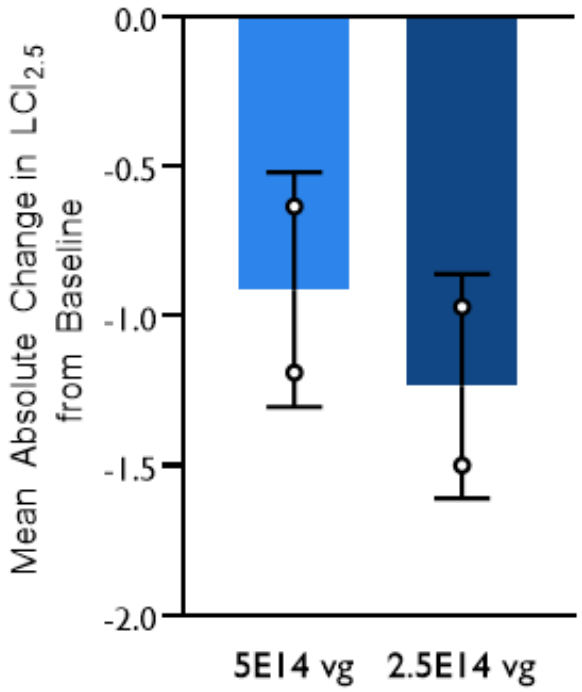
Clinical Activity: Mean Change in $ppFEV_1$, $LCI_{2.5}$ & CFQ-R-R in Lower Dose Cohorts From Baseline Through 1 Year of Follow-up (Months 3 to 12*)

$ppFEV_1$



Phase 2 Dose

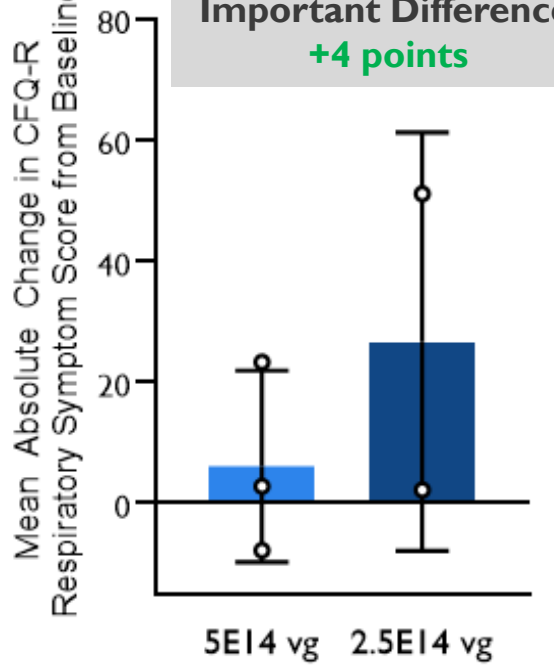
$LCI_{2.5}$



Phase 2 Dose

CFQ-R-R

Minimal Clinically Important Difference: +4 points



Phase 2 Dose

*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 1 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 1/2 clinical trial & program update expected H2 2026

THANK YOU

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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

Steps 2 & 3:
Therapeutic Vector Evolution

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)

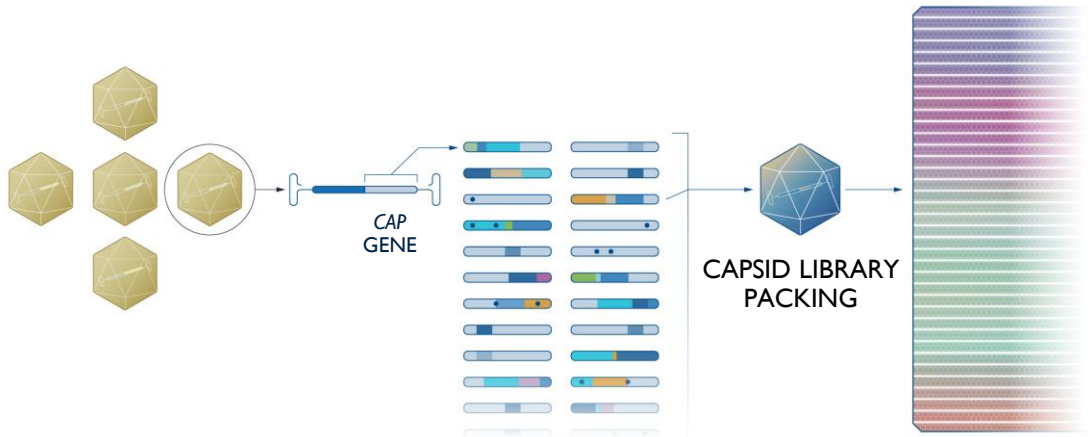
DESIGN ORGAN(S)-SPECIFIC **TARGET VECTOR PROFILE**

PACKAGE 4DMT AAV LIBRARIES

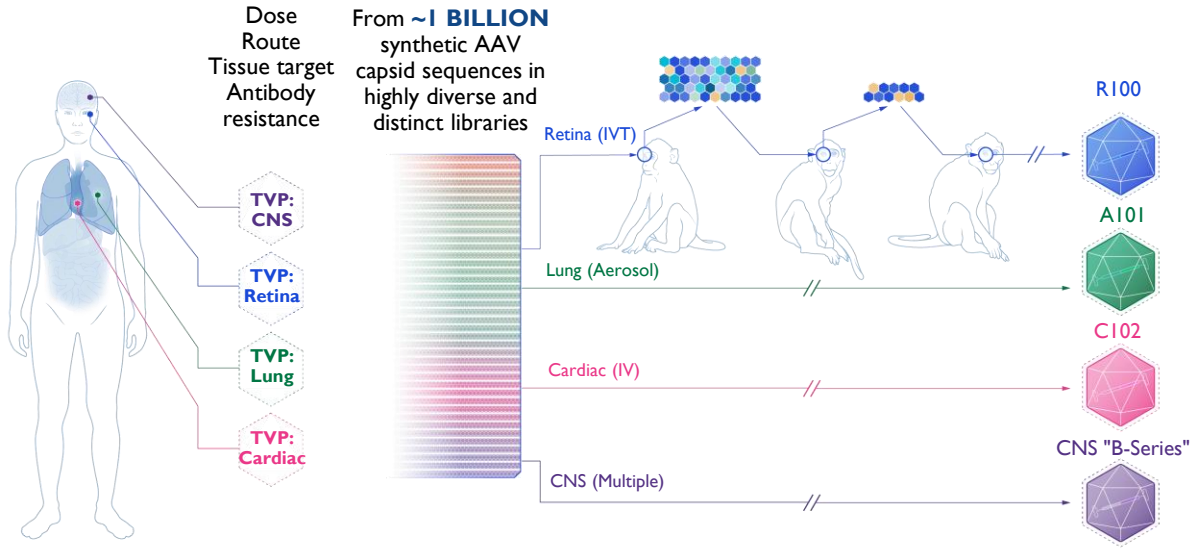
ADMINISTER 4DMT AAV LIBRARIES

COMPETITIVE SELECTION* TARGET VECTOR PROFILE FITNESS

LEAD VECTORS



Random peptide insertion - GH loop
Random point mutagenesis
Serotype shuffled
Ancestral reconstruction
Variable loop mutagenesis



*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

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