PRISM Phase 1/2 Study of 4D-150 in Wet AMD: 18-24 Months Extended Follow-Up, First Time Results

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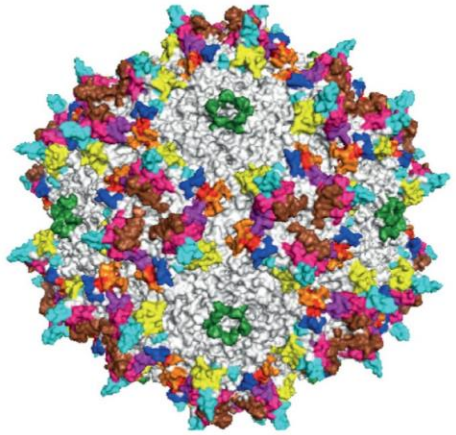
On behalf of the PRISM investigators

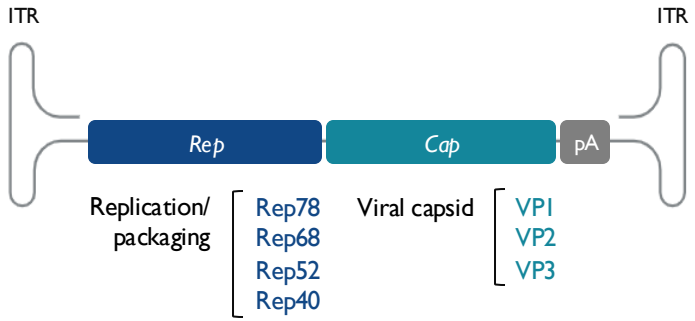
Disclosures

- Consultant: Bausch + Lomb, Genentech, Inc., Ocular Therapeutix, Zeiss;
- Investigator: 4D Molecular Therapeutics, Adverum, Allergan, Apellis, Astellas/AIRM, Aura, Aviceda, Chengdu Kanghong, Cognition, Eluminex, Genentech, Inc., Ionis, Kodiak Sciences, Mylan, NGM Bio, Ocular Therapeutix, Oxurion, Regeneron, Regenxbio, Stealth;
- Royalties: Bausch + Lomb, Harrow, Katalyst Surgical/Zeiss;
- Speakers Bureau: Genentech, Inc.

Adeno-associated Virus (AAV)

Leading Platform for the Delivery of Retina Gene Therapy





Advantages

- Non-pathogenic
- Relatively low immunogenicity
- Low risk of genotoxicity
- Stable long-term gene expression
- Highly amenable to bioengineering

Limitations

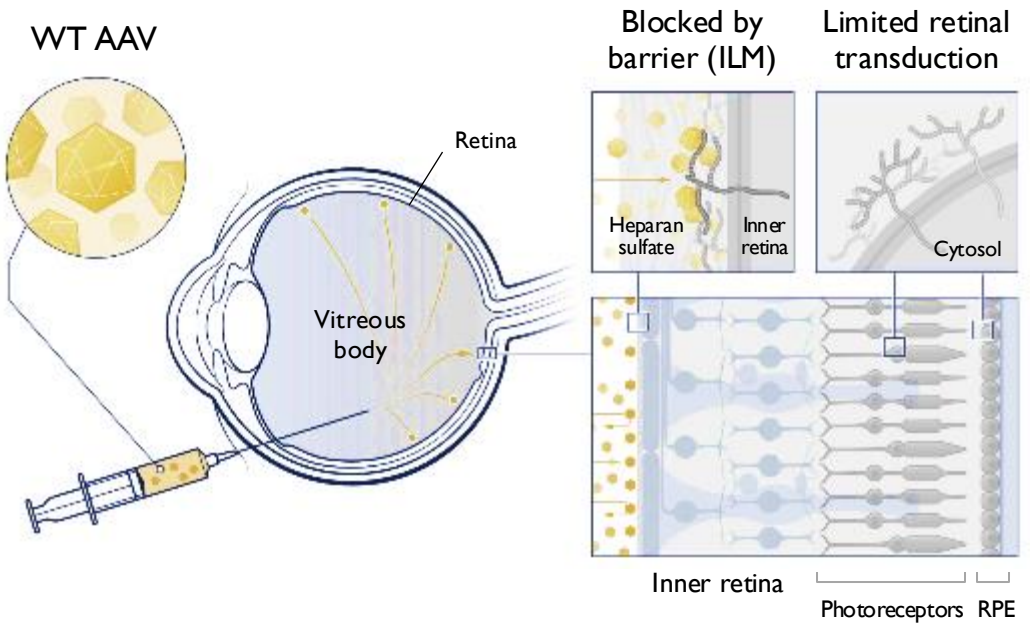
- Broad, non-specific tropism
  - Limited ability to target specific cell types
- Limited transduction efficiency
  - Higher doses/increased risk of AEs
- Susceptibility to pre-existing NAbs

AE, adverse event; ITR, inverted terminal repeat; NAb, neutralizing antibody; pA, polyadenylated tail.

Intravitreal AAV-based Retinal Gene Therapy

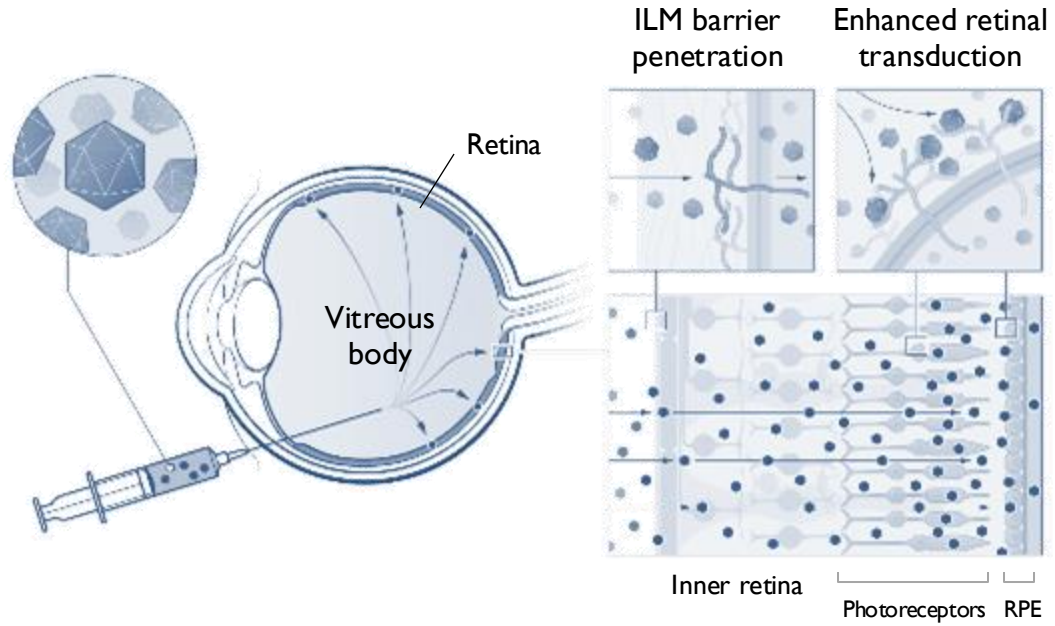
Key Challenge: Retinal Cell Transduction

Wild-type AAV



- Wild-type AAV vectors exhibit poor retinal penetration and transduction following IVI.

Optimal AAV Vector



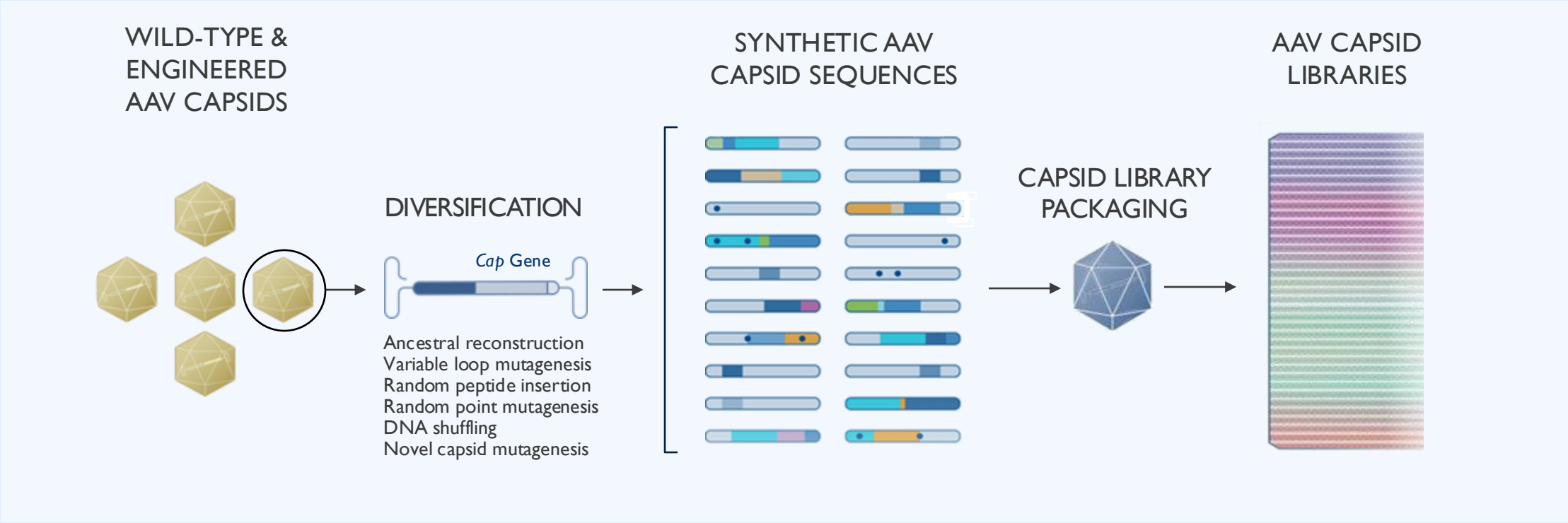
- Capacity to penetrate vitreoretinal barriers
- Transduction of all regions and layers of the retina

AAV, adeno-associated virus; ILM, inner limiting membrane; RPE, retinal pigment epithelium.

Therapeutic Vector Evolution

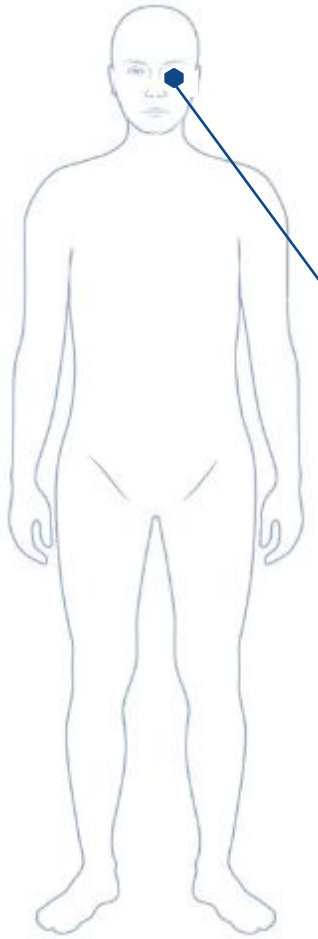
Directed Evolution-based Proprietary Vector Discovery Platform

- Define ideal vector profile (route of administration, dose, target cells, etc.)
- Multiple molecular biology techniques employed to generate massive genetic diversity



Ideal Vector Creation Overcomes Many Limitations

In Vivo Directed Evolution in Animal Models

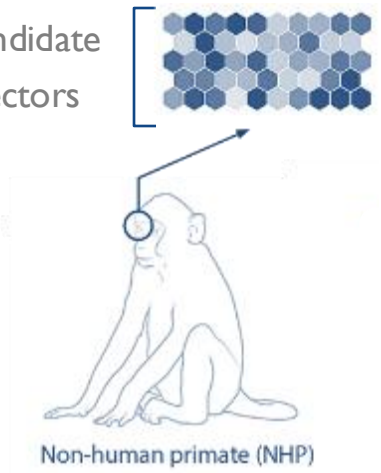


What must the ideal vector do?

Be **delivered at low doses** via **intravitreal injection** directly to all layers of **the retina**

How do you create the best vector?

Candidate vectors



Capsid selection based on:

- Best retinal penetration
- Lowest immune reaction
- Highest gene expression

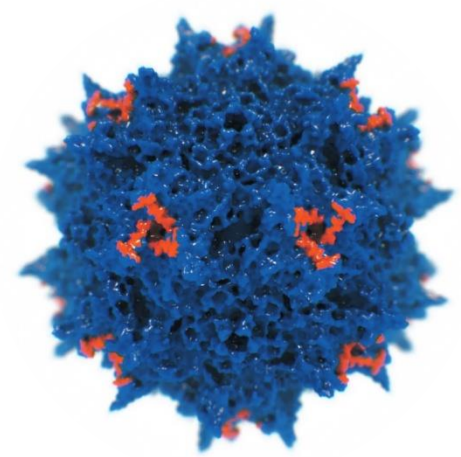
Iterative Competitive Selection

AAV, adeno-associated virus.

Calton MA, et al. Invest Ophthalmol Vis Sci. 2024;65:1.

4D-150: A Novel, R100-Based Dual-Transgene Investigational Gene Therapy

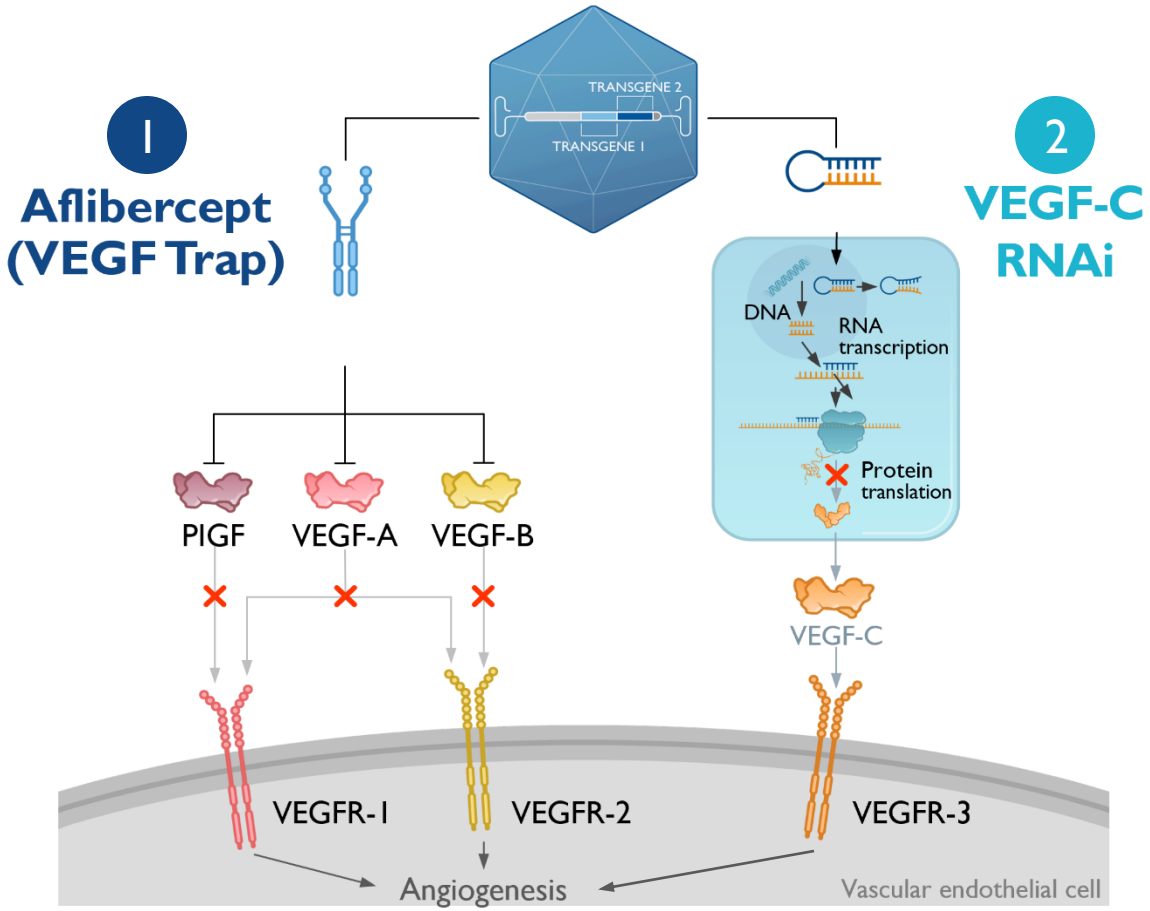
Delivery Vehicle: AAV Capsid (R100)



R100 AAV Capsid Specifically Designed to:

- Be administered via routine intravitreal injection
- Cross vitreoretinal barriers
- Selectively transduce cells of the retina

Dual Transgene Payload: 4D-150



AAV, adeno-associated virus; PIGF, placental growth factor; RNAi, ribonucleic acid interference; VEGF, vascular endothelial growth factor.

PRISM Phase 1/2 Clinical Trial

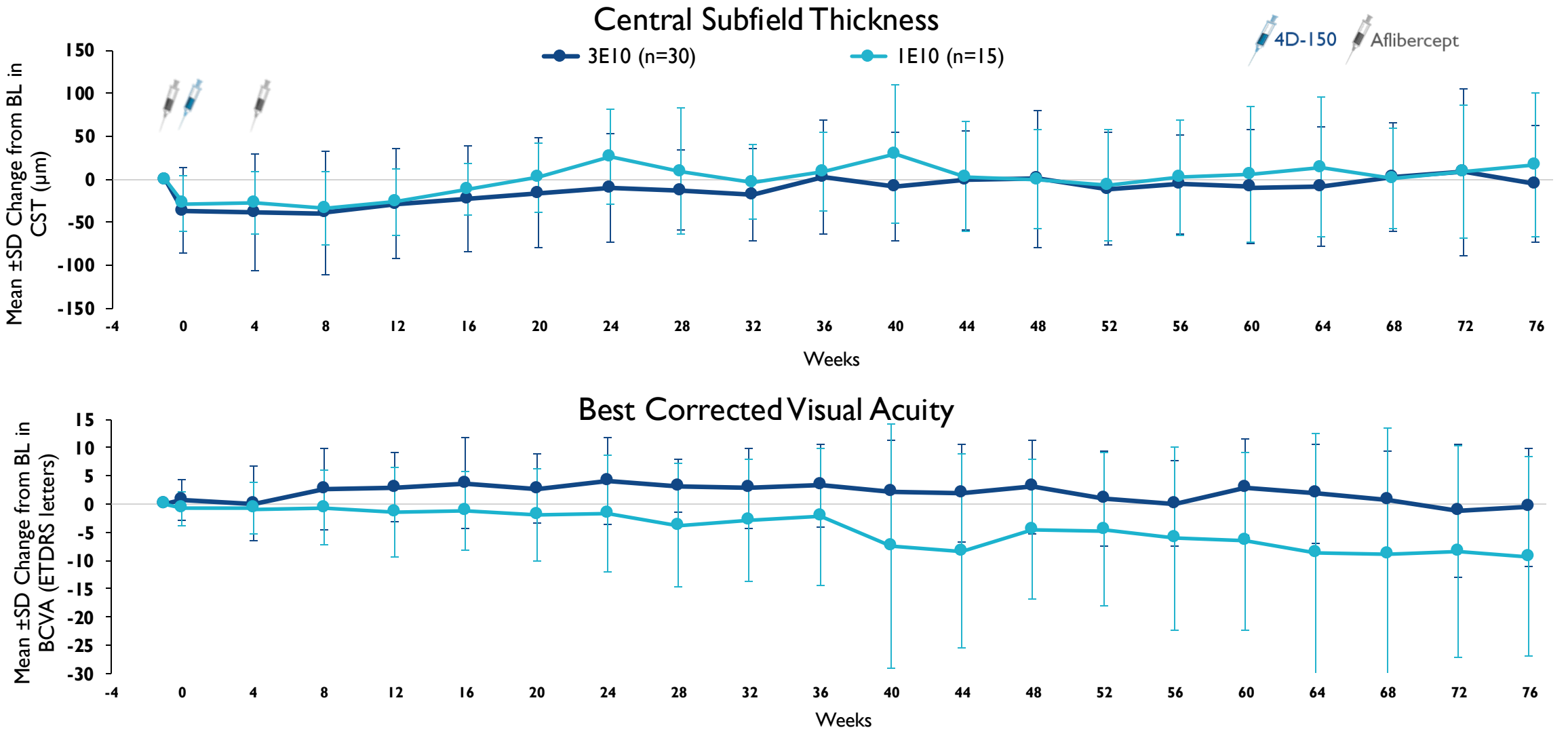
Evaluation of 4D-150 in Broad Range of nAMD Populations

Cohort	Phase 1 Dose Exploration	Phase 2a Dose Expansion	Phase 2b Population Extension
Population	Severe Disease Activity	Severe Disease Activity	Broad Population
Dose Groups	3E10 vg/eye (n=5) → 1E10 vg/eye (n=5) → 6E9 vg/eye (n=5); ◆ DSMC review	Randomized (2:2:1): 3E10 vg/eye (n=20); 1E10 vg/eye (n=21); AFLB 2 mg q8w (n=10)	Sequential: 3E10 vg/eye (n=30); 1E10 vg/eye (n=15)
Anti-VEGF Injections	≥6 in prior 12 months	≥6 in prior 12 months	1–6 in prior 12 m (≥1 last 12 weeks)
CST (screening)	≥300 µm or retinal fluid	≥325 µm and retinal fluid	No minimum or maximum
BCVA (screening)	25–78 ETDRS letters	34–83 ETDRS letters	34–83 ETDRS letters

AFLB, aflibercept; BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study.

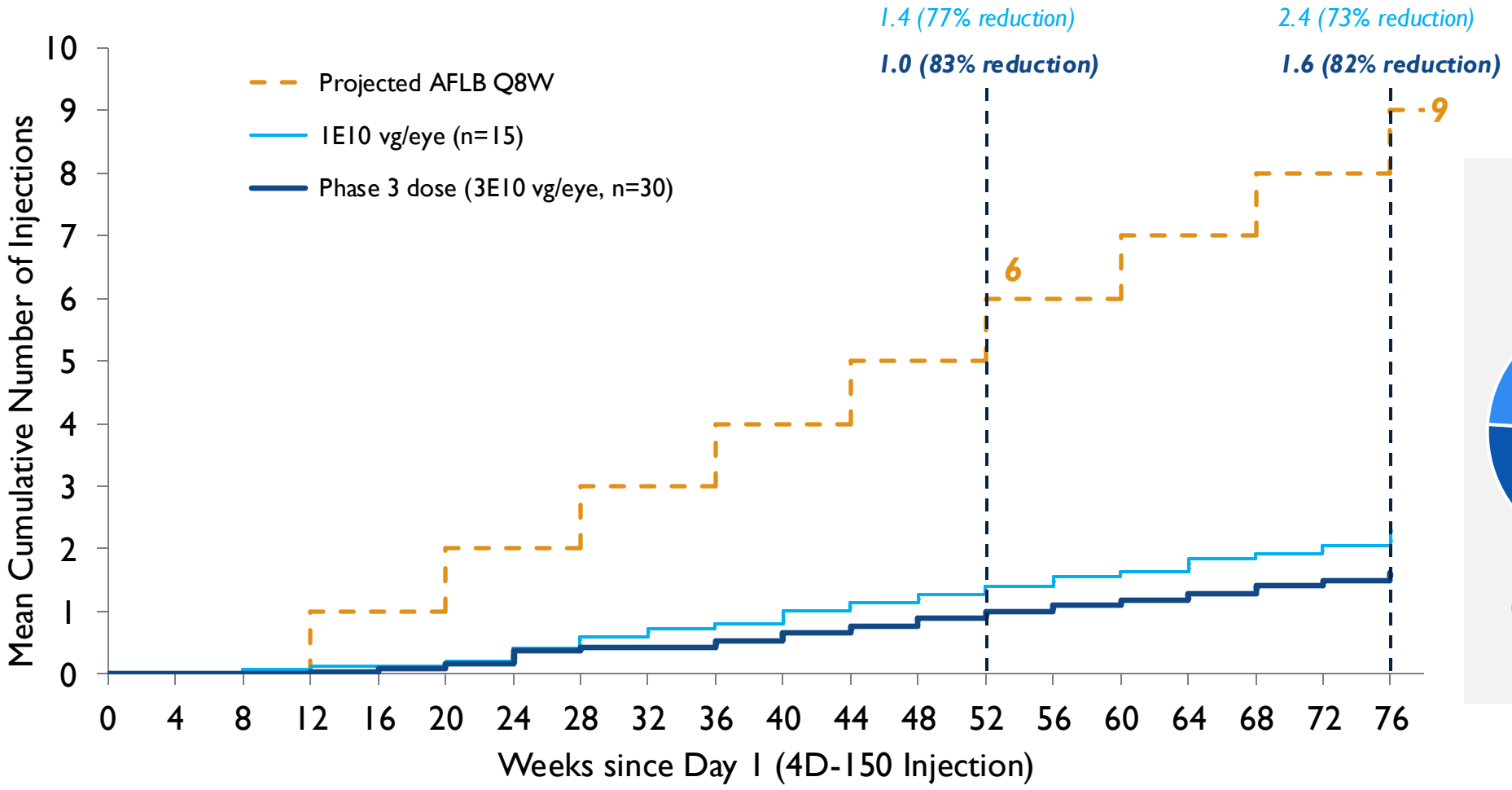
4D-150 in a Broad AMD Population: Phase 2b

18 Month Results

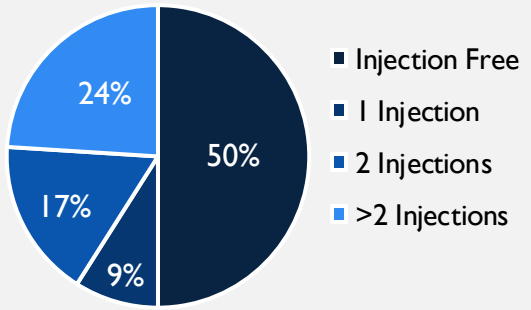


AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study

3E10 vs. 1E10 vg/eye: Consistent Dose Response in Mean Cumulative Supplemental Injections Through 1.5 Years



Supplemental Injections Over 1.5 Years (Phase 3 Dose)

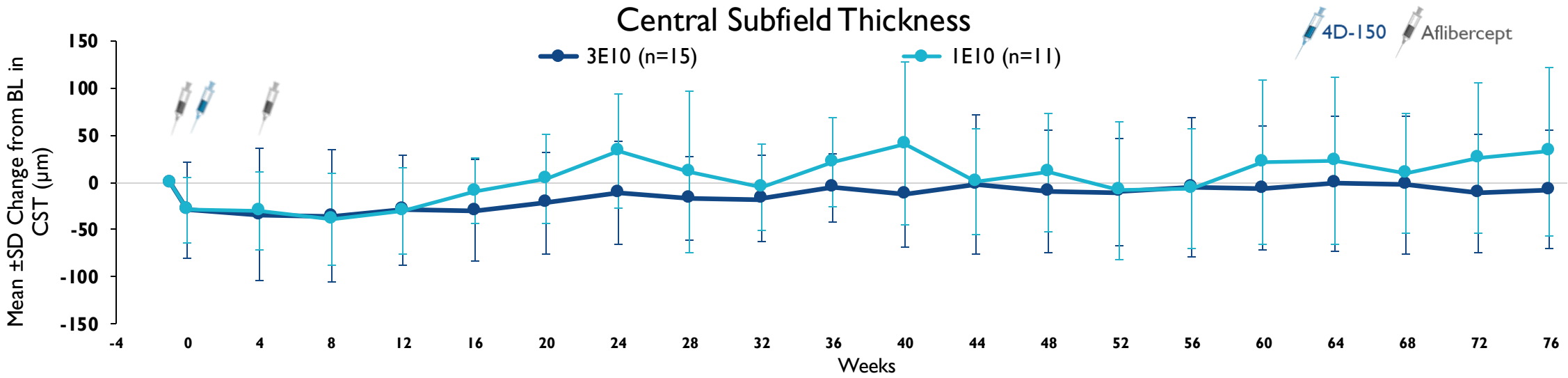


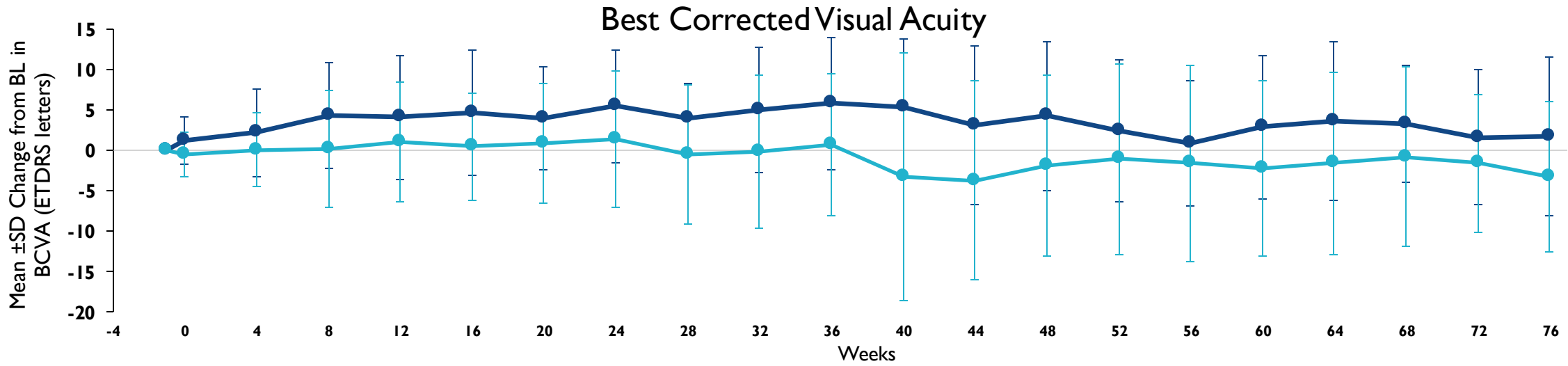
76% received 2 or fewer injections over 1.5 years

Data cutoff of August 22, 2025.
MCF, mean cumulative function derived from a single-arm Cox proportional hazard regression model. Projection based on approved dosing schedule for aflibercept in wet AMD after loading doses.

4D-150 in a Broad AMD Population: Phase 2b Recently Diagnosed (≤ 6 Months) Subgroup

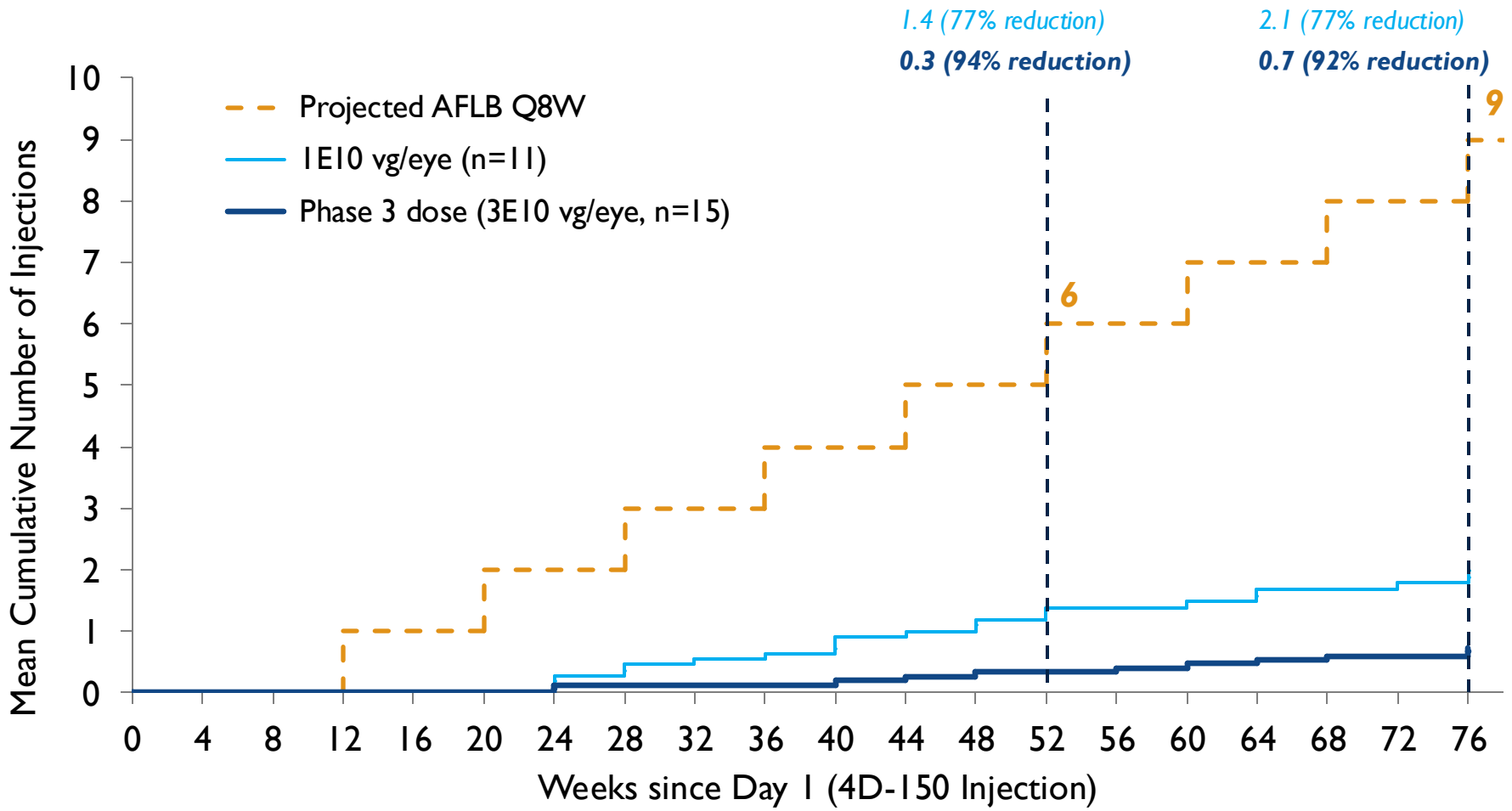
18 Month Results

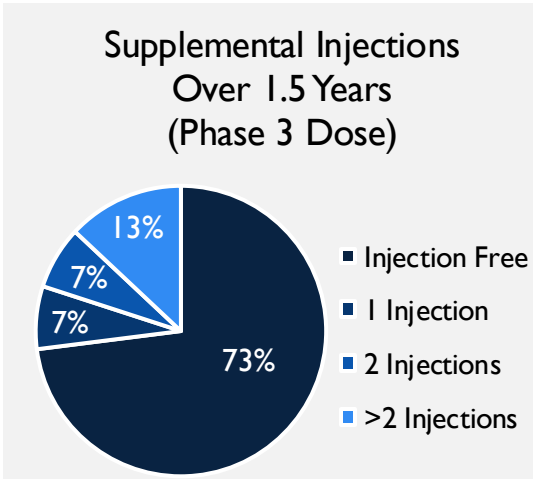




AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study

3E10 vs. 1E10 vg/eye: Consistent Dose Response in Mean Cumulative Supplemental Injections Through 1.5 Years





87% received 2 or fewer injections over 1.5 years

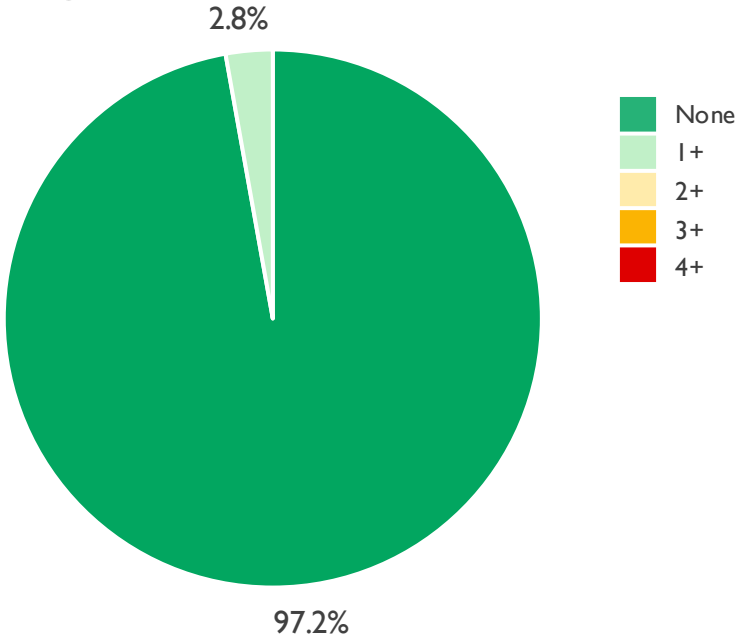
Data cutoff of August 22, 2025.
MCF, mean cumulative function derived from a single-arm Cox proportional hazard regression model. Projection based on approved dosing schedule for aflibercept in wet AMD after loading doses.

4D-150 Continues to be Well Tolerated

- No 4D-150–related serious adverse events
- No 4D-150–related hypotony, endophthalmitis, occlusive/non-occlusive retinal vasculitis, or choroidal effusions
- 4D-150–related intraocular inflammation (SUN/NEI):
  - Through Week 28 post-4D-150: **1+** vitreous cells at a single timepoint in 2 of 71 (**2.8%**), as previously reported*
  - After Week 28 post-4D-150: **No inflammation reported**
  - **99%** (70 of 71) completed prophylactic topical steroid taper on schedule
  - **99%** (70 of 71) remain completely off steroids

4D-150 3E10 vg/eye (N=71)*

Highest SUN/NEI Score†



Patients have reached
1.5 to 3.5+ years of follow-up

Data cutoff of August 22, 2025.
†4D-150–related. *One case at Week 4 and one case at Week 28.
Intraocular inflammation defined as presence of ≥1 anterior chamber or vitreous white blood cells on SUN/NEI scale.
NEI, National Eye Institute; SUN, Standardization of Uveitis Nomenclature.

4D-150 PRISM Phase 1/2 Update: 1.5- & 2-Year Follow-up

PRISM

Key Takeaways

Consistent, Durable and Clinically Meaningful Clinical Activity through 1.5 & 2 Years

- Visual acuity & anatomic control **maintained**
- **Durable reduction in injection number** across diverse wet AMD populations:
  - **79% reduction in a recalcitrant population**
  - **82% reduction in a broad population**
  - **92% reduction in a recently diagnosed* subgroup**
- **Strong dose response** favoring Phase 3 dose (3E10 vg/eye)

No New Safety or IOI Events

- No related SAE, hypotony, vasculitis, hypotony, endophthalmitis, occlusive/non-occlusive retinal vasculitis, or choroidal effusions
- Phase 3 dose (3E10 vg/eye, N=71):
  - **No new intraocular inflammation (IOI) since last update**
  - **Overall, no IOI in 97.2%**
  - **Through 28 weeks:** 2 cases of mild, transient IOI, *as previously reported*
  - **From after 28 weeks through 3.5 years+: No IOI**

Data cutoff as of August 22, 2025.
*Disease duration ≤0.5 years.
AMD, age-related macular degeneration

Global 4FRONT Phase 3 Wet AMD Program: Evaluating the Efficacy, Safety, and Durability of a Single IVT Injection of 4D-150 vs. Aflibercept 2mg Q8W

Primary Objective | Demonstrate non-inferiority in the mean change in BCVA from baseline to Week 52 of a single injection of 4D-150 compared to aflibercept 2mg (Q8W) after three aflibercept doses

Costs for both trials to be shared Otsuka

4FRONT-1

North America
N=400

100% Treatment naïve

Initiated in March 2025

4FRONT-2

Global
N=400

60% Treatment naïve; 40% Previously treated
(1-4 prior injections, diagnosed within 6 months)

Initiated in June 2025

Primary 52-week topline data expected:
4FRONT-1 in **H1 2027** & 4FRONT-2 in **H2 2027**

Key Inclusion Criteria

BCVA:
25-78 letters

Active disease

CST:
≤500 µm

Anti-VEGF responsive

CST, central subfield thickness; BCVA, best corrected visual acuity; VEGF, vascular endothelial growth factor.

Thank you!