4DMT

Intravitreal 4D-150

Randomized Phase 2 Dose Expansion in Wet AMD Patients with Severe Disease Activity & High Treatment Burden

PRISM

February 3, 2024 | *Webcast: February 5, 2024*

Forward-Looking Statements

This Presentation contains forward looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Presentation, including statements regarding our clinical development plans, strategy, future operations, future financial position, prospects, plans, and objectives of management, are forward looking statements. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "target," "should," "would," and similar expressions are intended to identify forward looking statements, although not all forward looking statements contain these identifying words. We may not actually achieve the plans, intentions, or expectations disclosed in these forward looking statements, and you should not place undue reliance on these forward looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward looking statements. In addition, the forward looking statements included in this Presentation represent our views as of the date of this Presentation. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward looking statements in the future, we specifically disclaim any obligation to do so. These forward looking statements should not be relied upon as representing our views as of any date subsequent to the date of this Presentation.

This Presentation discusses our product candidates that are under preclinical study and in clinical trials, and which have not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of our product candidates for the therapeutic use for which they are being studied.

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4DMT

Unlocking the Full Potential of Genetic Medicines to Treat Large Market Diseases

- Wet AMD is the **leading cause of vision loss** in the elderly impacting **~3M patients** in U.S. and Europe; drives **>$18B retinal diseases opportunity**

- 4D-150 is the **first IVT gene therapy product with a dual transgene payload** targeting four VEGF family members; **potential to be transformative** in the wet AMD market
  - ✓ R100 vector invented for single, low dose intravitreal (IVT) delivery to retina

- **Positive PRISM Phase 2 interim 24-week results** in patients with **severe disease activity & high treatment burden**
  - ✓ **Favorable** safety profile with **no significant or recurrent intraocular inflammation**
  - ✓ Stable BCVA & CST with **improved retinal anatomical control**
  - ✓ **89% overall reduction** in treatment burden, **84%** patients received 0-1 injections, **63%** were injection-free with **high dose 4D-150** (3E10 vg/eye)

- FDA RMAT and EMA PRIME designations enable **rapid Phase 3 development plan** with program initiation expected **in Q1 2025**

- **Strong Balance Sheet: ~$300M** estimated cash as of December 31, 2023

4D-150 Clinical Program Overview: Wet AMD & DME

Favorable Safety Profile & No Significant Inflammation Reported to Date (N=110)

INDICATION	PATIENT POPULATION	PHASE 2 TRIALS	ENROLLMENT STATUS (PATIENTS DOSED)	PHASE 3 TRIAL
Neovascular (wet) Age-Related Macular Degeneration (AMD)	Severe Disease & High Treatment Burden	PRISM Dose Exploration & Expansion	**Complete** (N=15 & 41) **Follow-up: up to 104 weeks**	Target Initiation **Q1 2025**
	Broad	PRISM Population Extension	**Complete** (N=32) **Follow-up: up to 20 weeks**	
Diabetic Macular Edema (DME)	Broad	SPECTRA Part 1: Dose Confirmation	**Complete** (N=22) **Follow-up: up to 8 weeks**	*tbd*
		SPECTRA Part 2: Dose Expansion	Pending (N=54)	

Data cutoff date, January 19, 2024

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4D-150

A Potential Treatment for Wet AMD with **Multi-Year Disease Control** & **Vision Preservation** with a **Single** IVT Injection

Significant Need to Overcome Limitations of Standard of Care Anti-VEGF Therapeutic Regimens for Wet AMD

1

~80% of physicians cite therapeutic **durability** as the greatest unmet need [1]

Leads to chronic undertreatment

2

Oscillating peak-trough anti-VEGF concentrations between injections can lead to **variability in CST**

Leads to CST variability associated with vision loss, fibrosis & geographic atrophy[2,3]

3

Treatment with VEGF-A inhibitors results in **increased VEGF-C levels in the eye**[4]

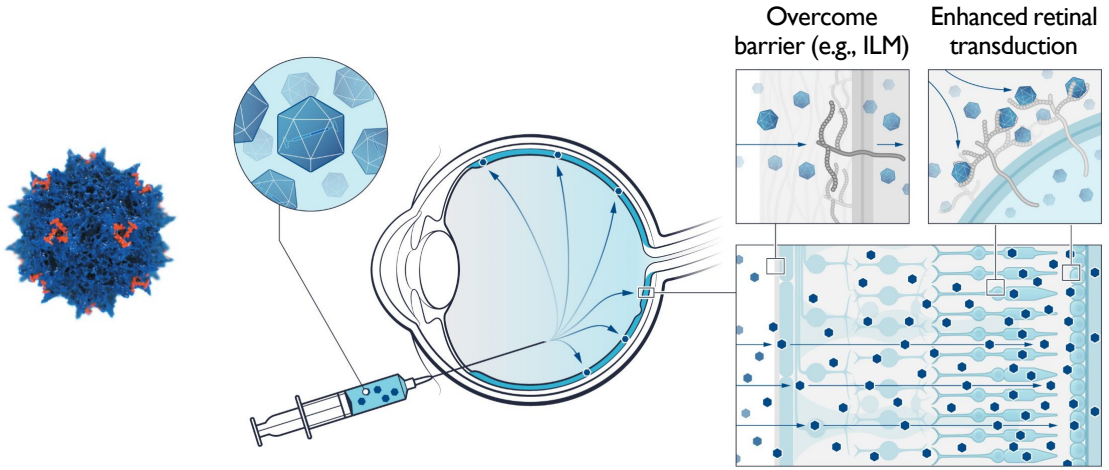
Upregulation of VEGF-C may contribute to treatment resistance[4–6]

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

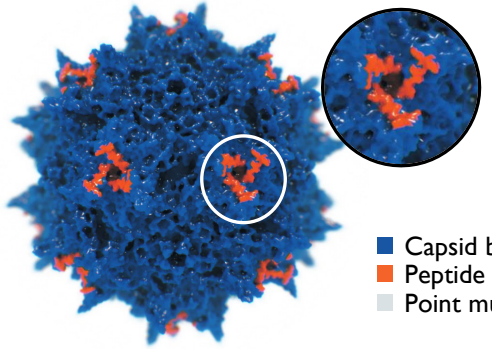
1. 2023 ASRS PAT survey. 2. Guo et al. *Ophthal Res* 2023; 66:406-12. 3. Evans et al. *JAMA Ophtalmol* 2020;138:1043-51. 4. Cabral et al. *Ophthalmol Retina* 2018;2:31-7. 5. Cao et al. *Circ Res* 2004;94:664-70. 6. Pongsachareonnont et al. *Clin Ophthalmol*. 2018;12:1877-85.
CRT, central retinal thickness.

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

R100

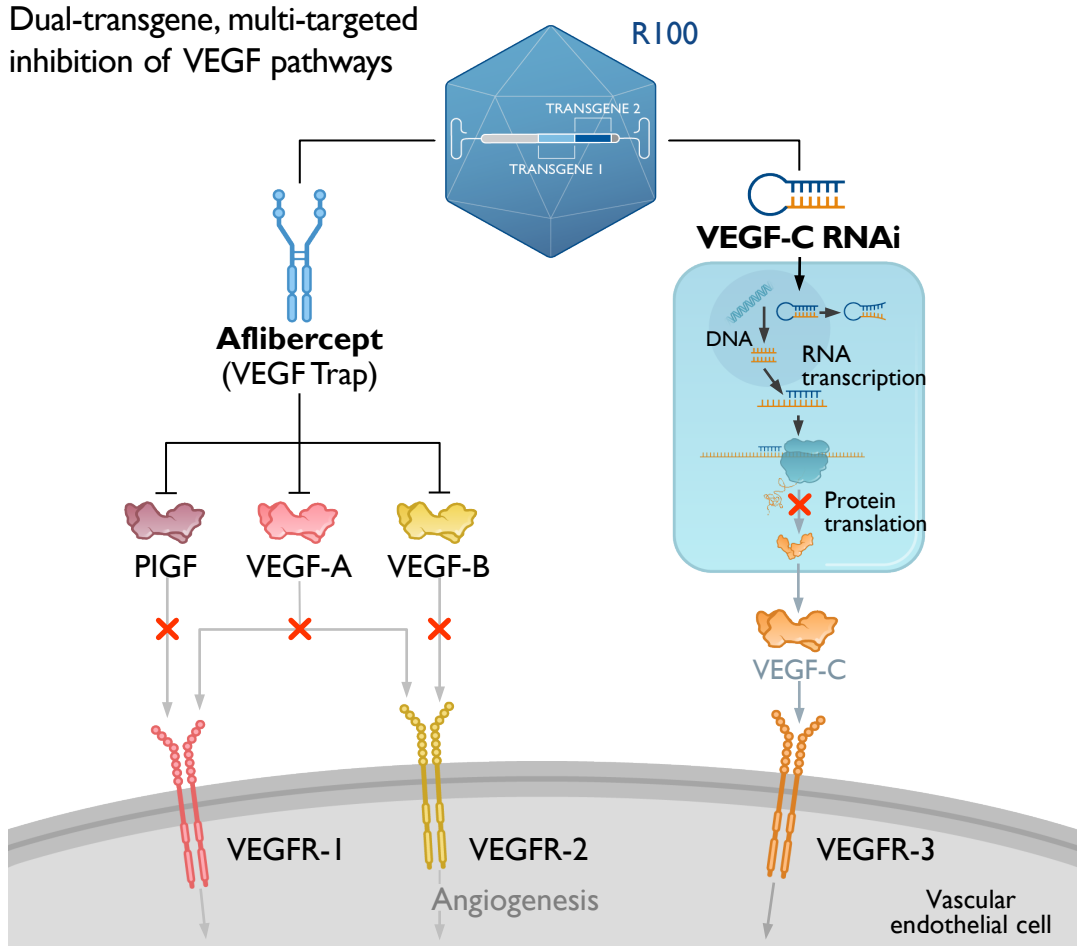


R100 Capsid

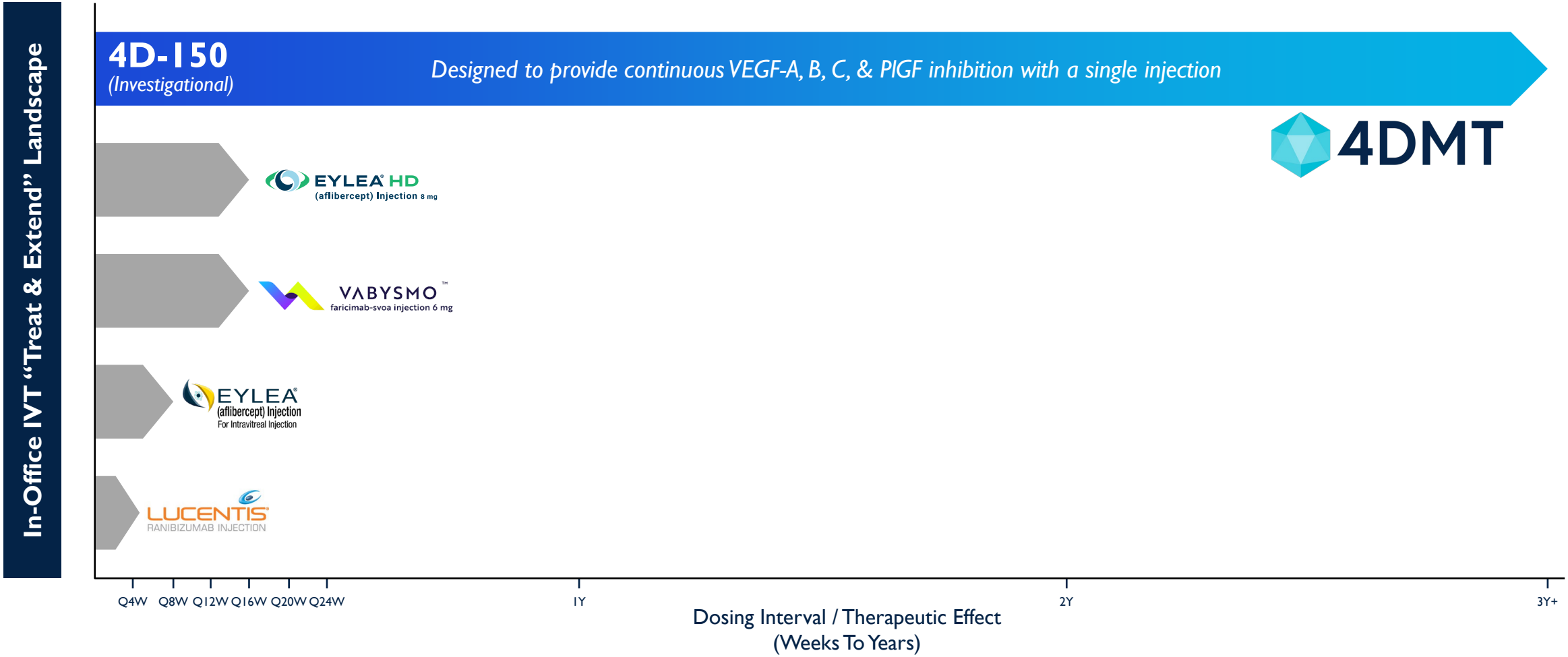


Abbreviations: ILM, inner limiting membrane; NHP, nonhuman primate; RPE, retinal pigment epithelium.

4D-150



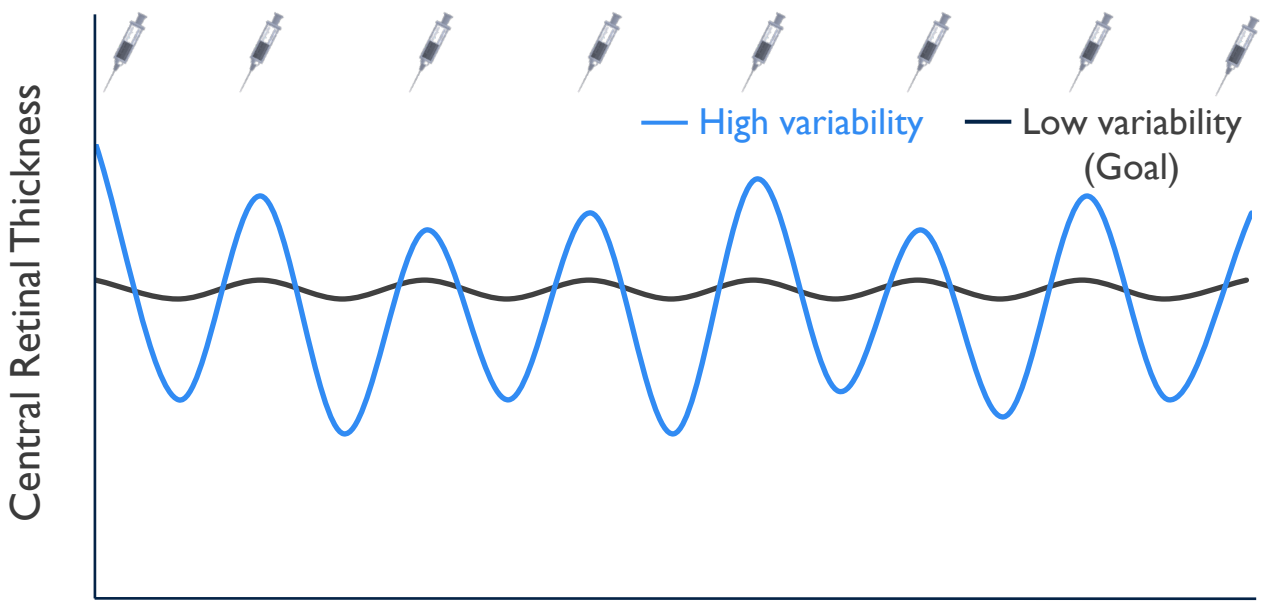
4D-150 Solution: Multi-Year Durability with a Single IVT Injection



FDA labeling.

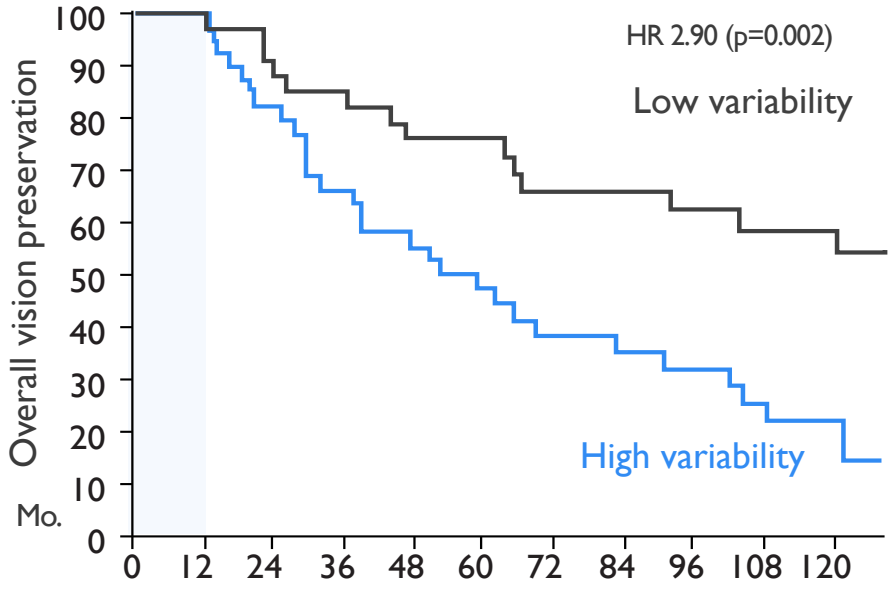
4D-150 Solution: Continuous Retinal Expression of Anti-VEGF to Reduce Retinal Anatomy Variability

Oscillating Peak-Trough Anti-VEGF Concentrations Can Lead to Variability in CST



Illustrative anti-VEGF treatment response

Central Subfield Thickness (CST) Variability Predicts Legal Blindness in Wet AMD[1]



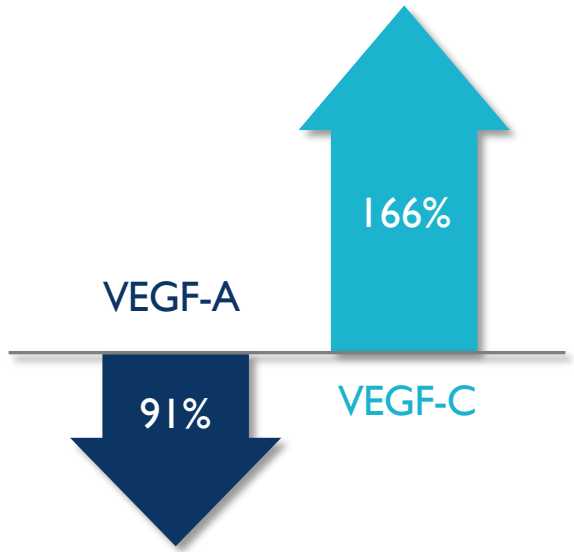
*Higher CRT variability during the first year of treatment is associated with **greater vision loss**[1] & **fibrosis**[2]*

1. Guo et al. *Ophthal Res* 2023; 66:406-12. 2. Evans et al. *JAMA Ophtalmol* 2020;138:1043-51. High variability: coefficient ≥20% in first year. Overall visual preservation rate: time from first injection to legal blindness (≤35 ETDRS letters). CRT, central retinal thickness.

4D-150 Solution: Dual-Transgene Payload Targeting 4 VEGF Family Members (VEGF-A, -B, -C & PlGF)

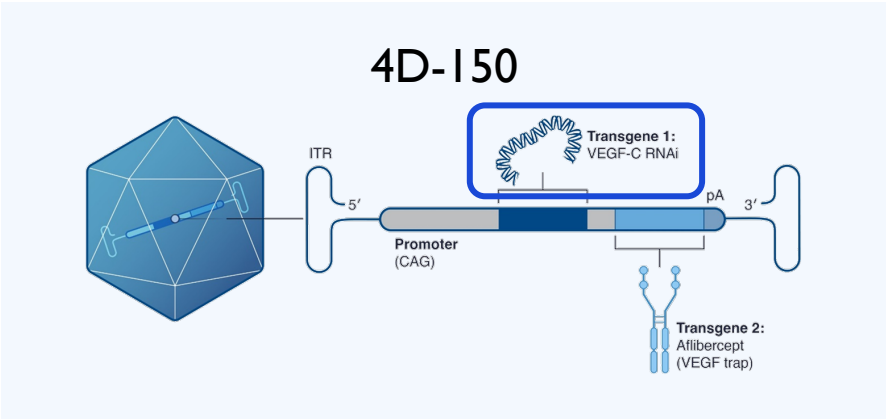
Biological Rationale for Targeting VEGF-C

Aqueous Concentrations Following Bevacizumab Injections[1]*



- Highly expressed in human RPE choroidal neovascular membranes[2]
- Stimulates endothelial cell proliferation and migration, vascular permeability[3–6]
- Upregulated by inhibition of VEGF-A[1,7,8]
- Potential anti-VEGF escape mechanism

4D-150: Dual-Transgene Payload



- Aflibercept
  Inhibits VEGF-A, VEGF-B, & PlGF
- VEGF-C miRNA
  Inhibits expression of VEGF-C

1. Cabral et al. *Ophthalmol Retina* 2018;2:31–7. 2. Otani A et al. *Microvasc Res* 2002;64:162–9. 2. Hsu MC et al *Cells* 2019;8. 3. Joukov et al. *EMBO J* 1996;15:290–8. 4. Joukov et al. *J Cell Physiol* 1997;173:211–15. 5. Cao Ret al. *Circ Res* 2004;94:664–70. 6. Puddu et al. *Mol Vis* 2012; 18:2509–177. Pongsachareonnont P et al. *Clin Ophthalmol* 20187;12:1877–85. 9. Jackson TL et al. *Ophthalmology* 2023 Feb 6: Epub. *2 months post administration of bevacizumab. RPE, retinal pigment epithelium.

4D-150 Poised to be Market Leader for VEGF-Driven Retinal Diseases

Designed to Address the Limitations of Current Therapeutic Regimens: VISION PRESERVATION

1

~80% of physicians cite therapeutic **durability** as the greatest unmet need [1]

✓ **Single** routine intravitreal injection provides durable clinical activity

2

Oscillating peak-trough anti-VEGF concentrations between injections can lead to **variability in CST**

✓ **Continuous** local expression of anti-VEGF transgenes to reduce CST variability

3

Treatment with VEGF-A inhibitors results in **increased VEGF-C levels in the eye**[2]

✓ **Dual** transgene payload targeting 4 VEGF family members (*VEGF-A, B, C & PlGF*)

Goal: **Vision Preservation** for Millions with a **Safe, Routine, One-time IVT Treatment**

1. 2023 ASRS PAT survey. 2. Cabral et al. *Ophthalmol Retina* 2018;2:31-7. CRT, central retinal thickness.

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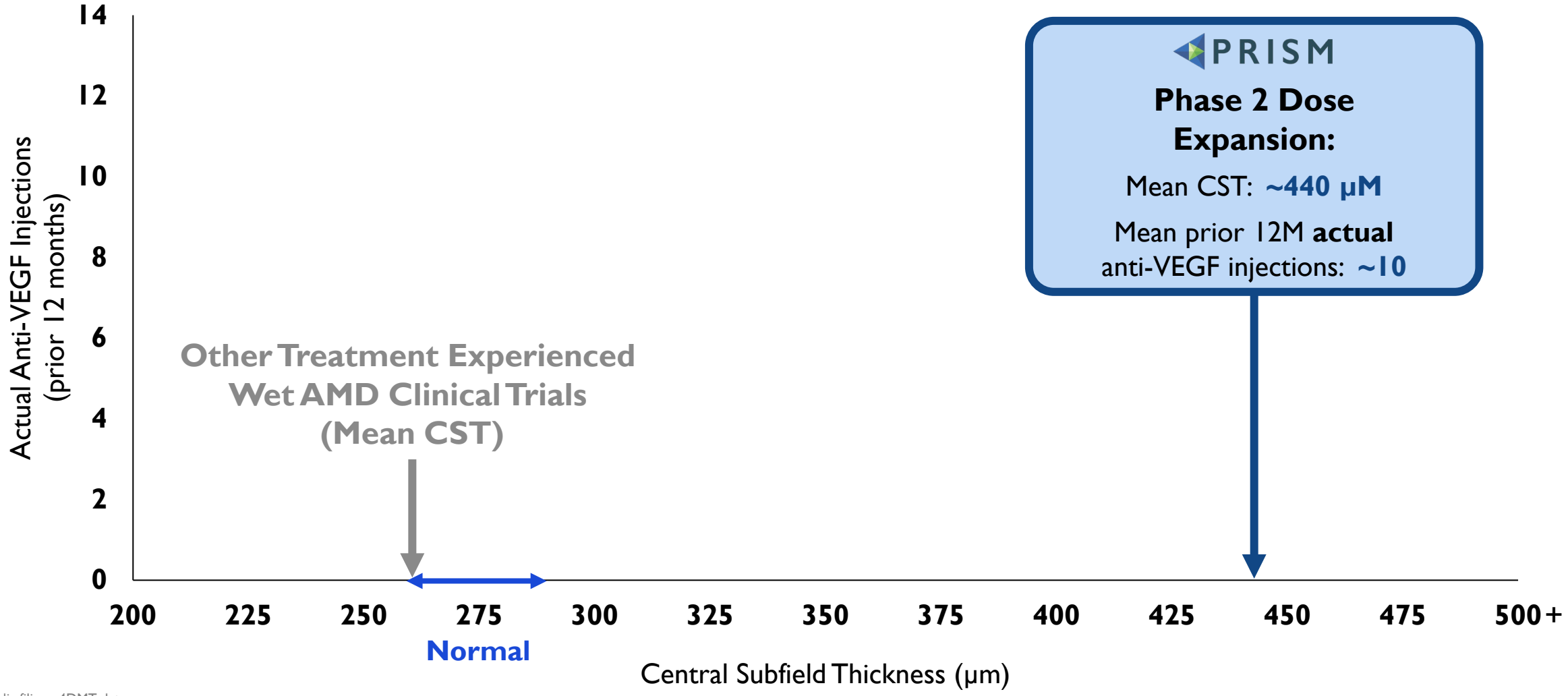
Randomized Phase 2 in Wet AMD Patients with **Severe Disease Activity & High Treatment Burden**

Trial Design & Baseline Characteristics

Focus on Wet AMD Patients with Severe Disease Activity (CST) & Highest Treatment Burden (Actual Injections in Prior 12 Months)



Public filings, 4DMT data.

Dose Expansion Cohort Design: Key Enrollment Criteria & Treatment Randomization

Designed for highest unmet need wet AMD patients based on disease activity (CST) & anti-VEGF injection treatment burden

Key Inclusion Criteria:

- **Anti-VEGF Injections prior 12 months:** ≥6
- **CST:** ≥325 µm **AND presence of subretinal or intraretinal fluid**
- **BCVA:** 34–83 ETDRS letters (20/200-20/25)

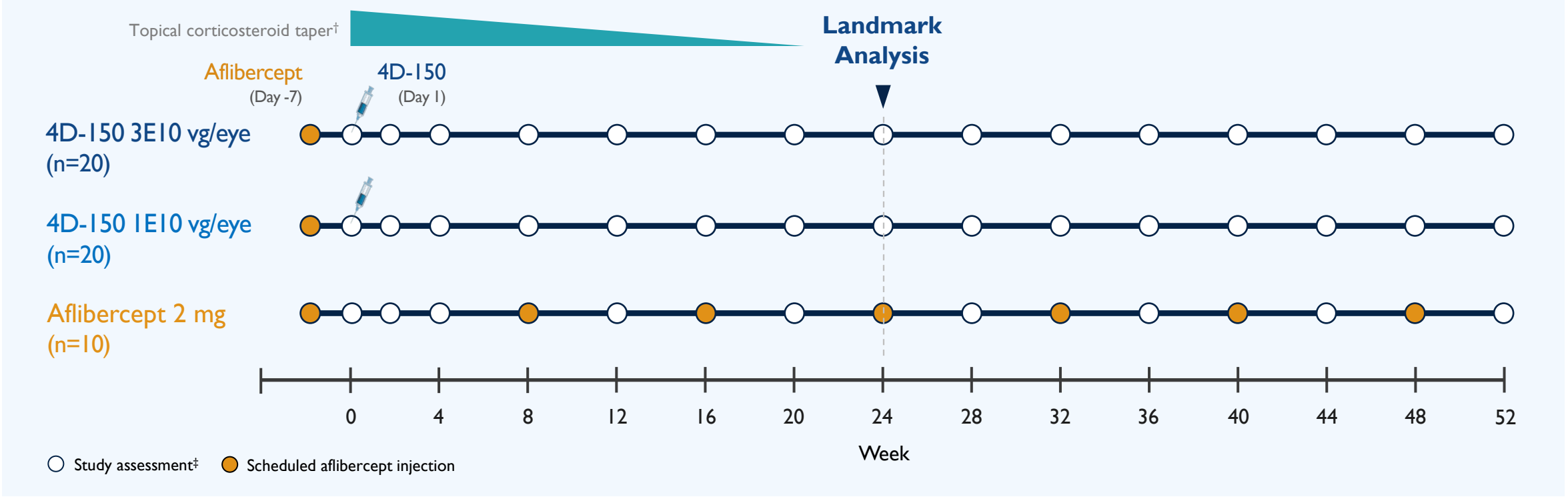
2:2:1

Randomized

- 3E10 vg/eye (n=20)
- 1E10 vg/eye (n=20)
- Aflibercept 2 mg (Q8W, n=10)

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

Treatment Schema & Endpoints: 4D-150 at Doses of 3E10 & 1E10 vg/eye vs. Aflibercept Q8 Week Control



Supplemental Injection Criteria

- BCVA: Loss of ≥10 letters from average of Day -7 & Day 1 measurement attributable to intraretinal or subretinal fluid
- CST: Increase ≥75 µm from average of Day -7 & Day 1 measurement
- New vision-threatening hemorrhage due to wet AMD per investigator

Key Endpoints

- Safety
- Annualized anti-VEGF injection rate*
- % requiring supplemental aflibercept
- ΔBCVA and ΔCST from baseline

*Powered to detect difference in anti-VEGF injections compared to aflibercept; study participants and site personnel masked to 4D-150 dose (treatment assignment to 4D-150 vs aflibercept not masked).
†Scheduled 20-week corticosteroid taper (4D-150 groups). ‡Visual acuity, optical coherence tomography, ophthalmic exam.

Baseline Characteristics: Wet AMD Patients with Severe Disease Activity & High Treatment Burden

	3E10 vg/eye (n=20)	1E10 vg/eye (n=21)	Aflibercept (n=10)	**Total (N=51)**
Mean ±SD age, years	77 ± 8.0	77 ± 8.6	80 ± 4.1	77 ± 7.7 *(range: 57–92)*
Mean ±SD time since diagnosis, years (% ≥3 years)	4.0 ± 3.0 (60%)	2.9 ± 2.2 (33%)	1.9 ± 1.5 (20%)	3.1 ± 2.5 (41%) *(range: 0.7–11.1)*
Mean ±SD BCVA, ETDRS letters	68 ± 11.3	71 ± 12.4	71 ± 13.2	70 ± 11.9 *(range: 35–87)*
Mean ±SD central subfield thickness, µm	429 ± 89.3	465 ± 114.1	419 ± 64.3	**442** ± 96.9 *(range: 295–816)*
Mean *annualized* anti-VEGF injections*	10.0	9.9	9.0	**9.8**
Mean ±SD *actual* anti-VEGF injections in prior 12 months*	9.9 ± 2.4	9.4 ± 2.1	9.3 ± 0.9	**9.6** ± 2.0 *(range: 7–14)*

*Includes Day -7 AFLB injection
Data cutoff date, January 19, 2024

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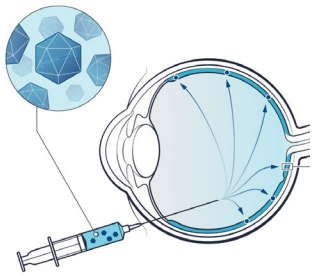
Randomized Phase 2 Clinical Trial in Wet AMD Patients with **Severe Disease Activity & High Treatment Burden**

Interim Data: 24 Week Landmark Results

PRISM Met All Objectives in Wet AMD Patients with Severe Disease Activity & High Treatment Burden Through 24 Weeks

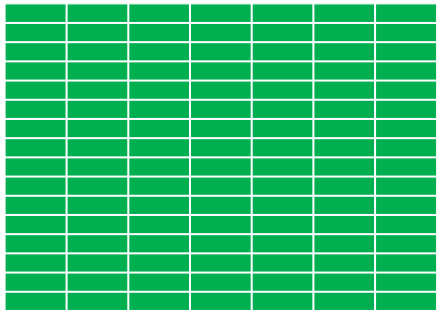
Administration

✓ **Single, routine** intravitreal injection



Safety

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



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

✓ **89%** overall reduction

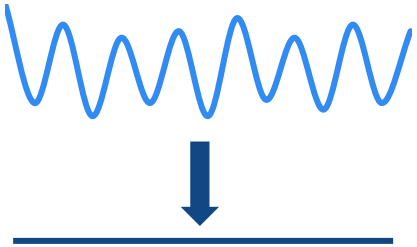
✓ **84%** 0–1 injections

✓ **63%** injection-free

Retinal Anatomical Control

✓ **Improved** retinal anatomical control

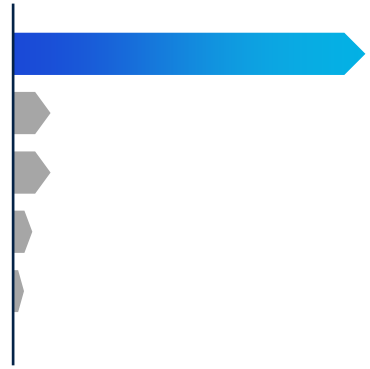
Retinal Thickness



Long Term Durability (3E10 vg/eye from Phase 1)

✓ **Multi-year** (up to 2 years) durability

Potential for long-term vision preservation



Data cutoff date, January 19, 2024

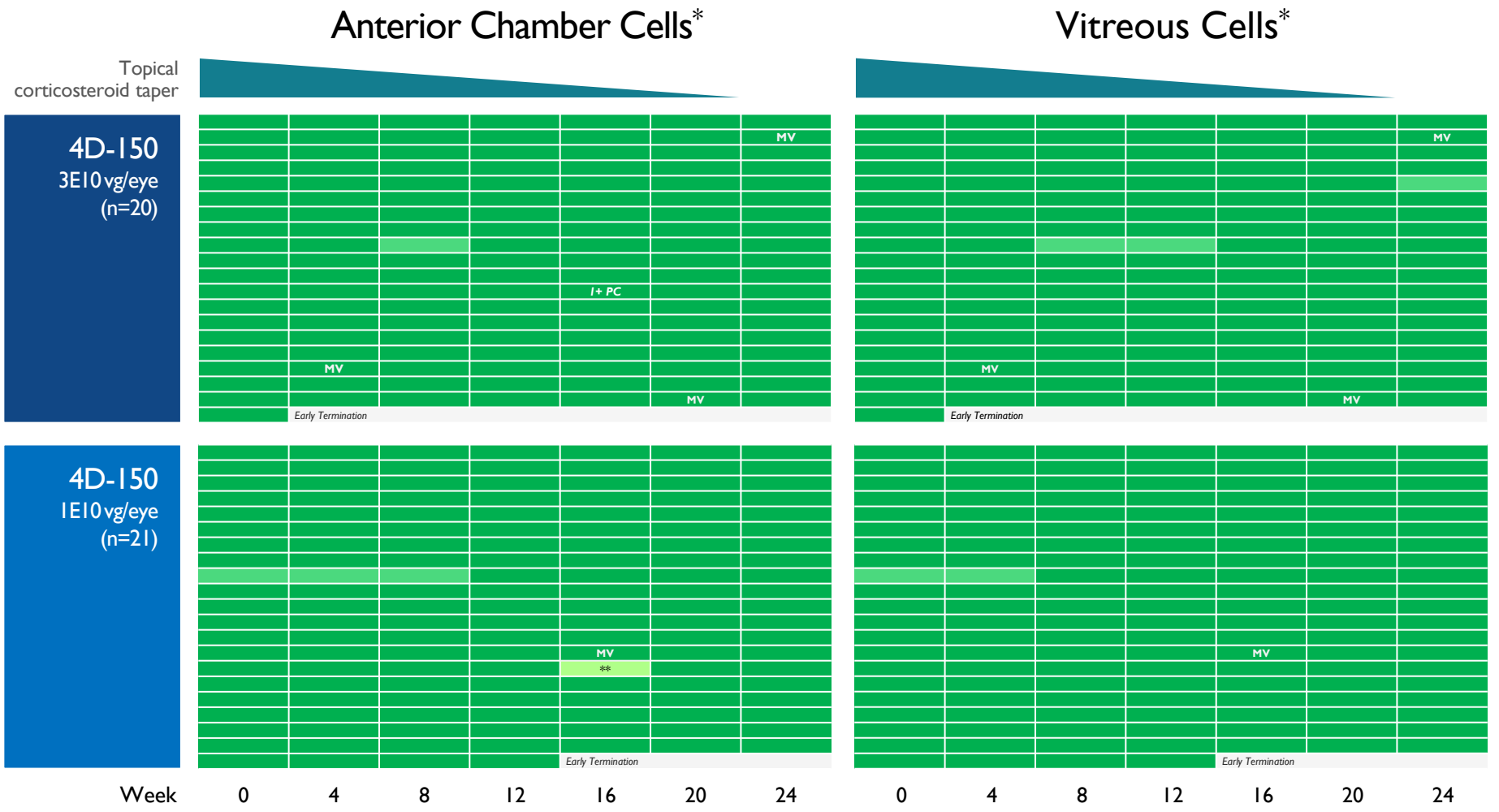
4D-150 Demonstrated Favorable Safety Profile to Date with No Significant or Recurrent Intraocular Inflammation

- **No significant intraocular inflammation***
  - **High dose (3E10 vg/eye): None**
  - **97% (38 of 39 patients) completed 20-week prophylactic topical corticosteroid taper on schedule**
  - Low dose: Single eye at week 16 had 1+ AC mixed (pigmented & white blood) cells and resolved by next visit; completed prophylactic topical corticosteroid taper by week 26
  - **All patients currently off steroids through up to 48 weeks of follow-up**
- No 4D-150–related SAEs or study eye SAEs
- No hypotony, endophthalmitis, retinal vasculitis, choroidal effusions, or retinal artery occlusions

Note: 2 patients died on study; PI assessed as not related to 4D-150 (3E10 vg/eye cohort: 1 subject died 38 days post 4D-150 IVT due to metastatic urothelial carcinoma;1E10 vg/eye cohort: 1 subject died 110 days post 4D-150 IVT due to acute myocardial infarction)

*SUN or NEI ≥1+ white blood cells on ophthalmic exam. AC, anterior chamber; SUN, Standardization of Uveitis Nomenclature; SAE, Severe Adverse Event.
Data cutoff date, January 19, 2024

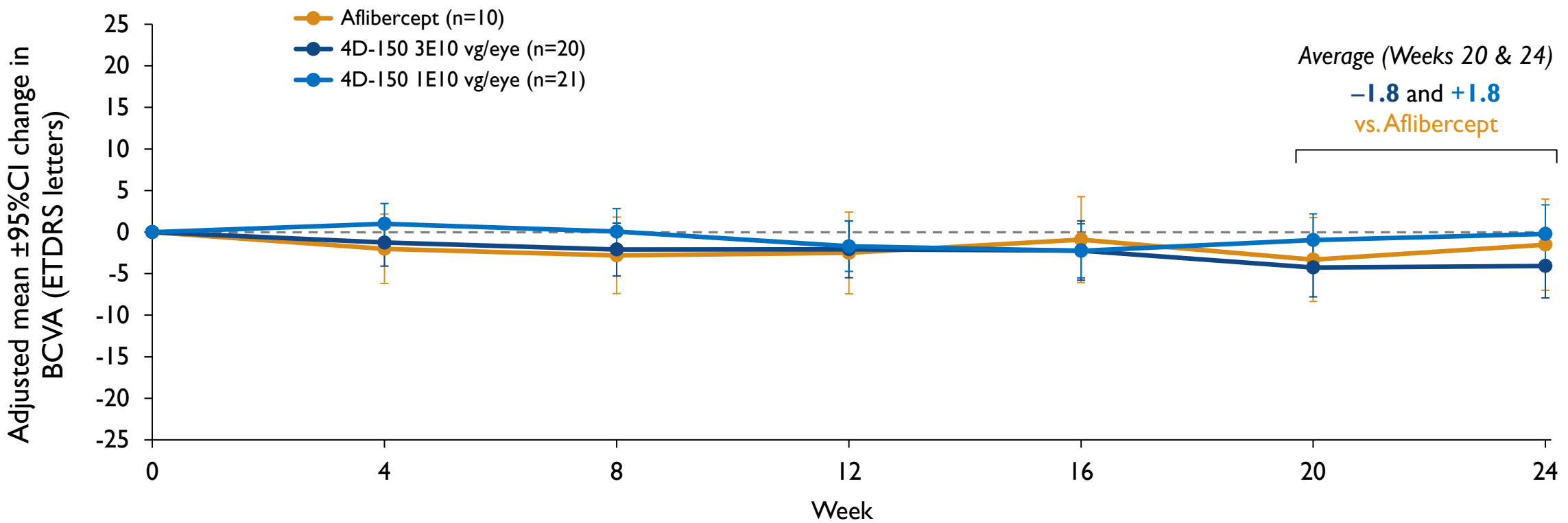
No Clinically Significant or Recurrent Intraocular Inflammation by Ophthalmic Examination



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

*SUN and NEI Scores for white blood cells. **Mixed WBC and pigmented cells; managed with temporary increase in topical corticosteroid dose (taper completed by Week 26).
MV, missed visit. NEI, National Eye Institute; SUN, Standardization of Uveitis Nomenclature. Data cutoff date, January 19, 2024

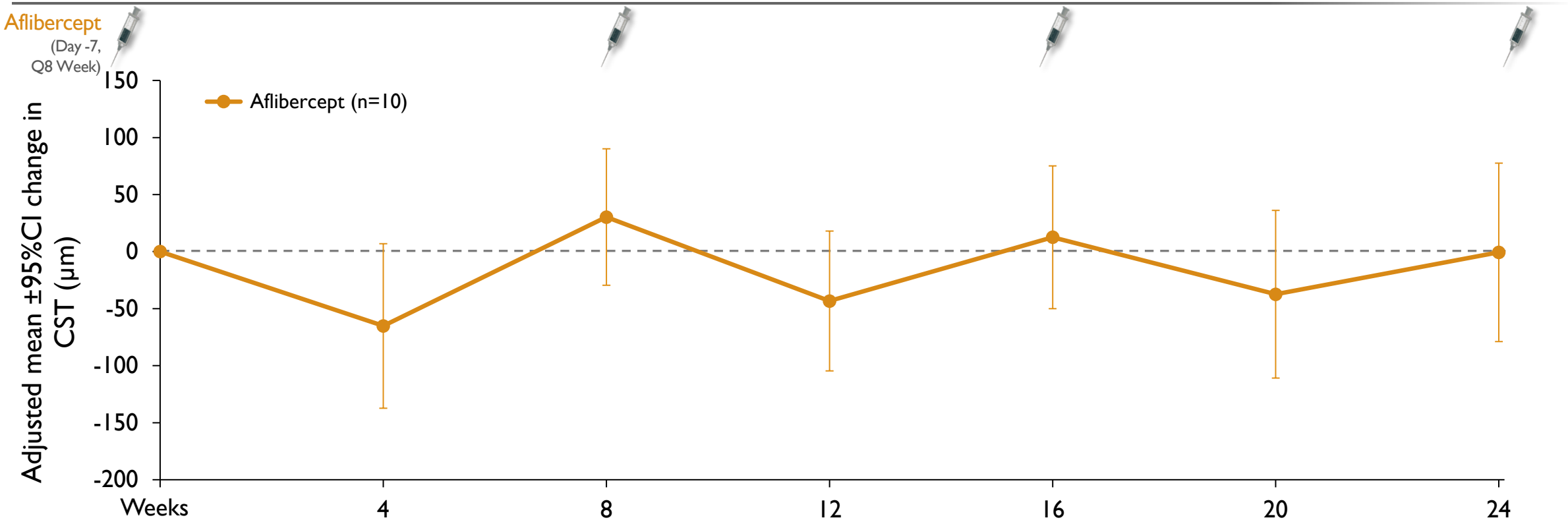
BCVA Equivalent & Stable Across All Arms in Severe Disease Activity Patients



Difference (95% CI) vs Aflibercept	Week 20	Week 24
4D-150 (3E10 vg/eye)	–1.0 (–7.2, 5.3)	–2.6 (–9.3, 4.2)
4D-150 (1E10 vg/eye)	2.3 (–3.6, 8.3)	1.3 (–5.2, 7.8)

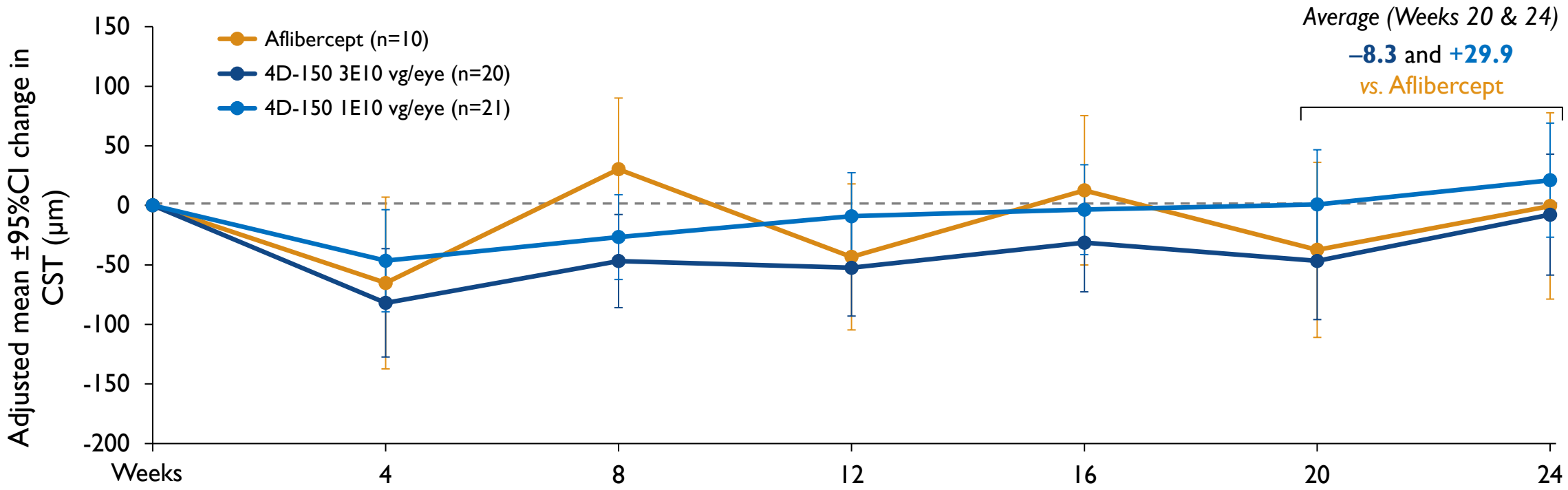
Baseline=Day -7. BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.
Adjusted mean, difference in adjusted mean and the associated 95% CI are estimated from a mixed–effect model for repeated measures (MMRM) including Weeks 4-24 data as observed without imputing missing values.
Data cutoff date, January 19, 2024

Considerable CST Variability Observed in Q8 Week Aflibercept Arm



Baseline=Day -7. Adjusted mean, difference in adjusted mean and 95% CI estimated from a mixed–effect model for repeated measures including observed data (weeks 4-24) without imputing missing values. CST, central subfield thickness.
Data cutoff date, January 19, 2024

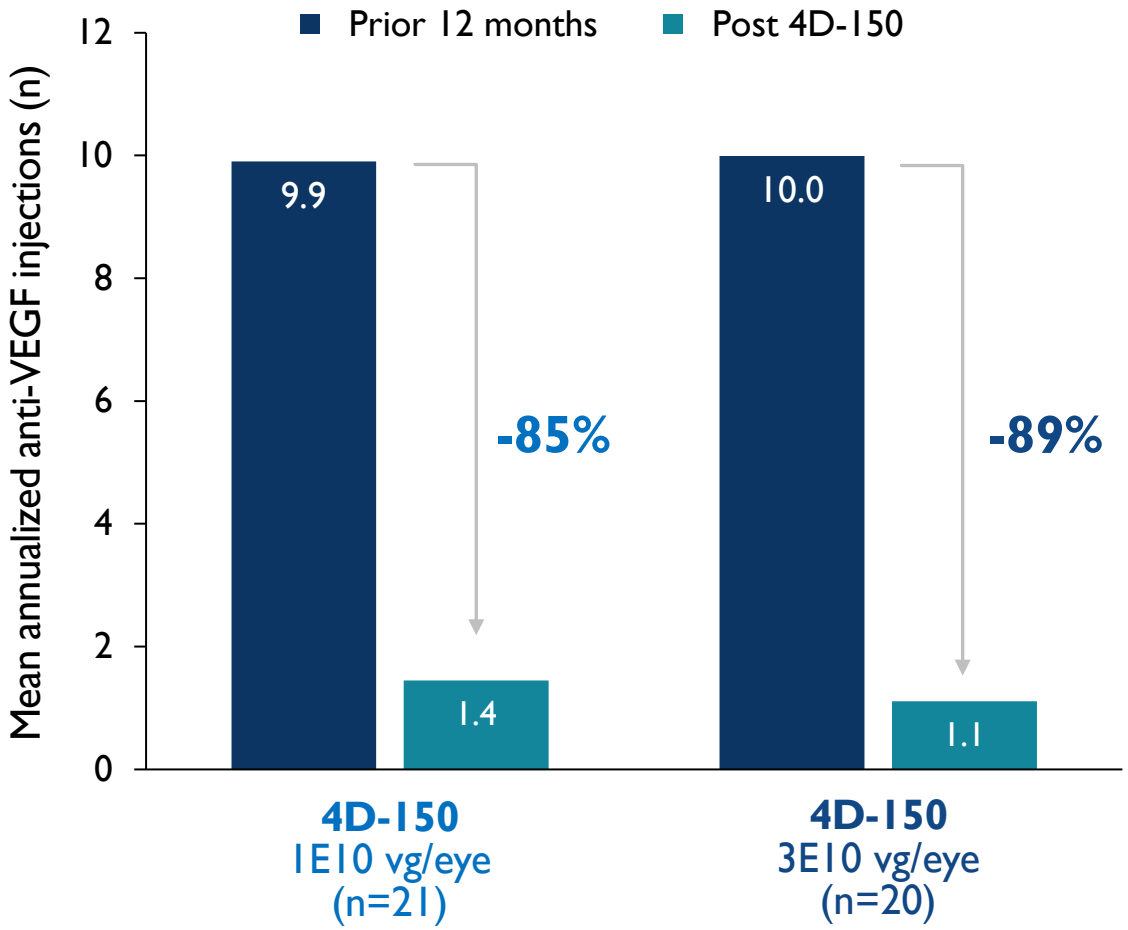
High Dose 4D-150: Strong Anatomic Control, Reduced CST Variability Compared to Aflibercept Arm



Difference (95% CI) vs Aflibercept	Week 20	Week 24
4D-150 (3E10 vg/eye)	–9.3 (–97.9, 79.3)	–7.3 (–101, 86.2)
4D-150 (1E10 vg/eye)	38.1 (–48.9, 125.2)	21.7 (–70.4, 113.8)

Baseline=Day -7. Adjusted mean, difference in adjusted mean and 95% CI estimated from a mixed–effect model for repeated measures including observed data (weeks 4-24) without imputing missing values. CST, central subfield thickness; CI, confidence interval. Data cutoff date, January 19, 2024

Robust Reduction in Treatment for Severe Disease Activity & High Treatment Burden Patients: 89% Reduction with High Dose 4D-150



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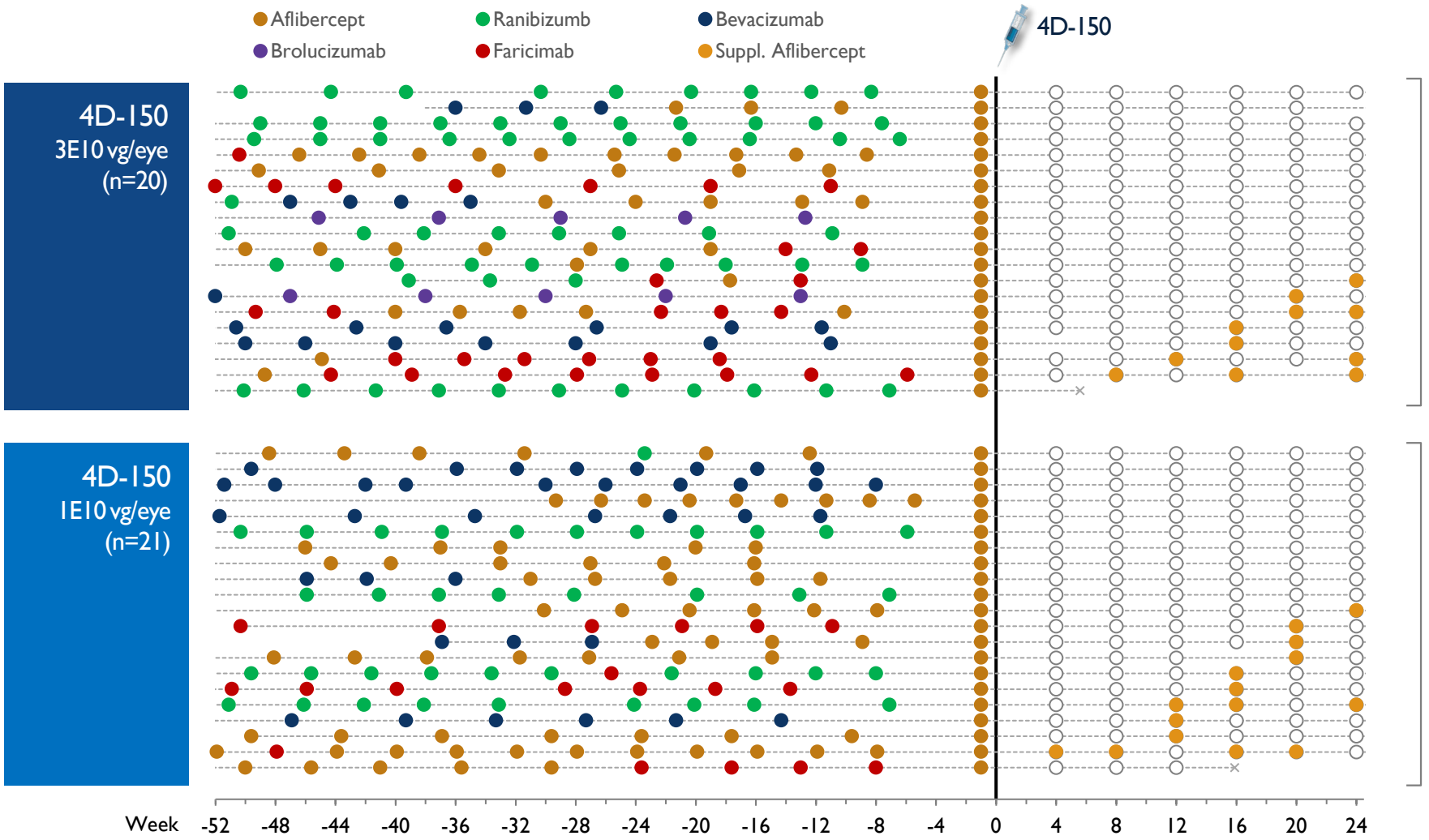
Robust Reduction in Treatment for Severe Disease Activity & High Treatment Burden Patients: 89% Reduction with High Dose 4D-150



89% reduction in annualized anti-VEGF injection rate

84% 0–1 injection

63% injection-free

85% reduction in annualized anti-VEGF injection rate

90% 0–1 injection

50% injection-free

Data cutoff date, January 19, 2024

PRISM Phase 1 Update: Tolerability & Durable Biological Activity Maintained for up to 104 Weeks in Injection-Free Patients

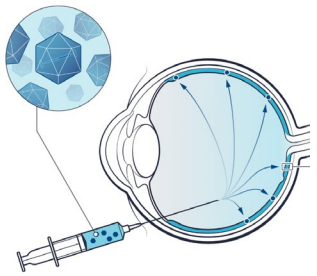
- **Safety (N=15)**: **maintained** (no new inflammation, no change in steroid status)
- **Durability of activity for 3E10 vg/eye injection-free patients (n=3):**
  - **All 3 patients remain injection-free**
    - Patient 1: through **104 weeks**
    - Patient 3: through **100 weeks**
    - Patient 4: through **80 weeks**

Data cutoff date, January 19, 2024

PRISM Met All Objectives in Wet AMD Patients with Severe Disease Activity & High Treatment Burden

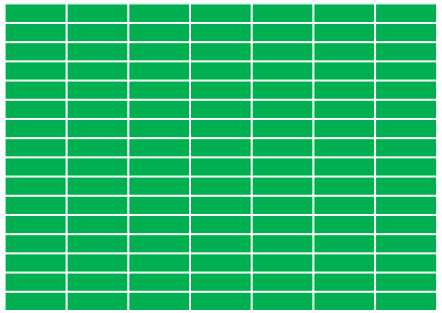
Administration

✓ **Single, routine** intravitreal injection



Safety

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



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

✓ **89%** overall reduction

✓ **84%** 0–1 injections

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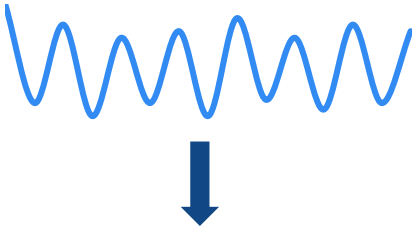
Retinal Anatomical Control

✓ **Improved** retinal anatomical control

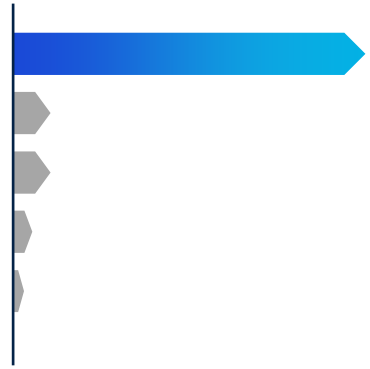
Retinal Thickness



Long Term Durability (3E10 vg/eye from Phase 1)

✓ **Multi-year** (up to 2 years) durability

Potential for long-term vision preservation



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4D-150 Next Steps in Development: Phase 2 Results Enable Phase 3

Phase 3 Planning

4D-150 Registrational Planning in Wet AMD

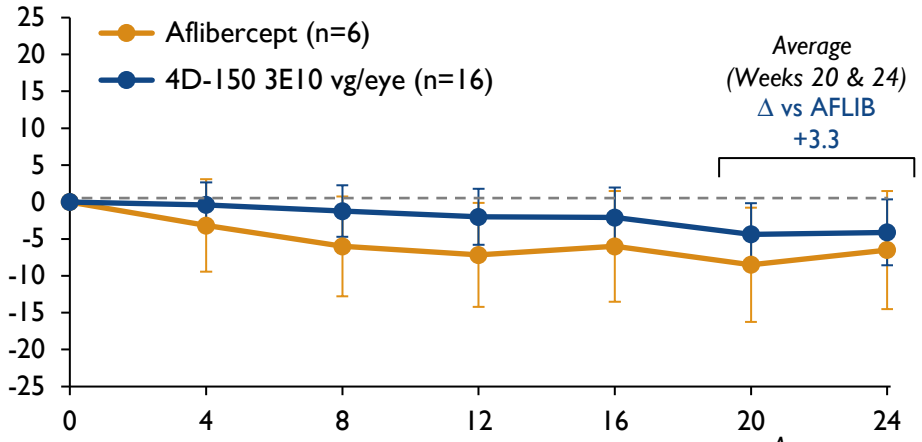
- **Phase 3 design based on initial feedback from FDA & EMA and clinical data to-date:**
  - Noninferiority (BCVA) 4D-150 **vs.** aflibercept 2mg Q8 week
  - **4D-150 3E10 vg/eye selected as study dose**
  - ~225 patients per arm
  - Broad wet AMD population, including patients with severe disease activity and high treatment burden
- **FDA RMAT & EMA PRIME Designations**
  - **Increased collaboration** between the FDA & EMA on regulatory approval planning
  - Opportunity for **expedited product development**
- Additional regulatory interactions planned in Q2 2024; **update expected in Q3 2024**
- **Expect to initiate Phase 3 program in Q1 2025**

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

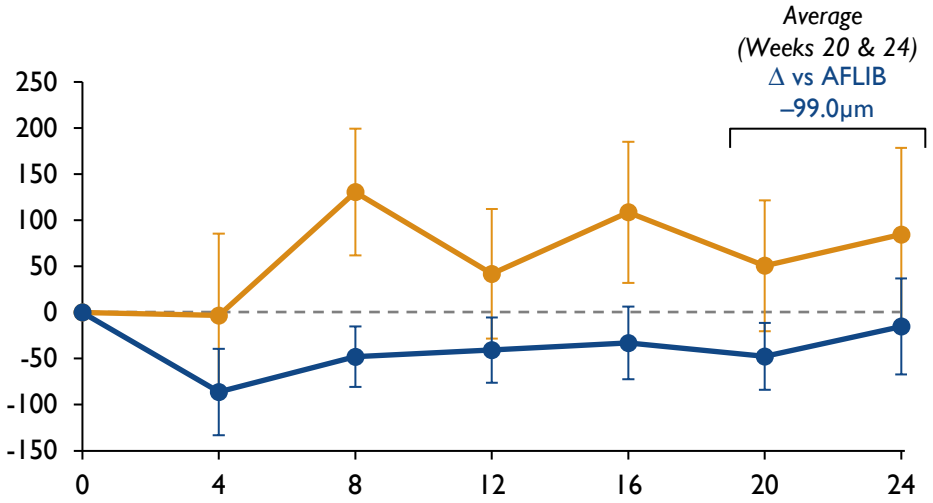
Preliminary Phase 3 Eligibility Criteria:

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

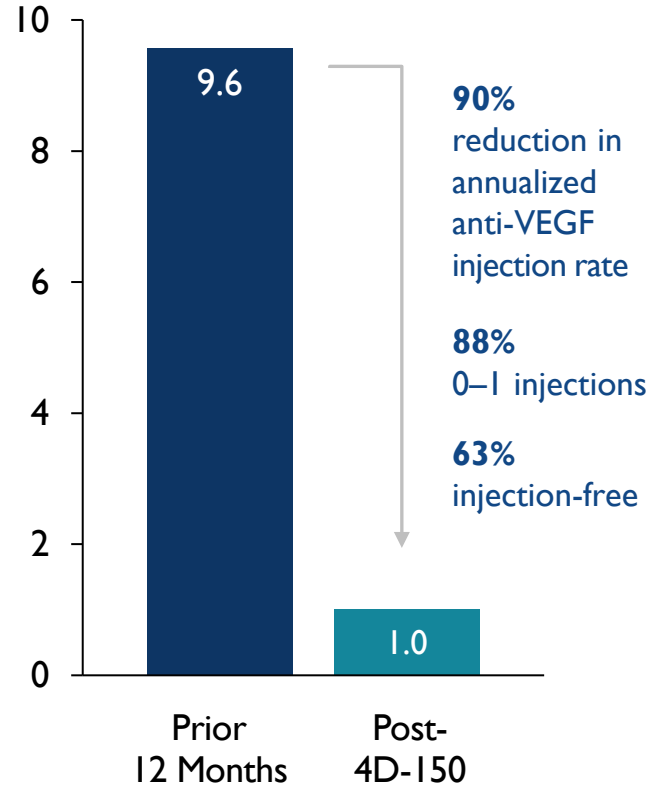
Adjusted mean ±95% CI change in BCVA (ETDRS letters)



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



Anti-VEGF Injections



Baseline=Day -7. Adjusted mean, difference in adjusted mean and the associated 95% CI are estimated from a mixed–effect model for repeated measures (MMRM) including Weeks 4-24 data as observed without imputing missing values. *Participants excluded based on BCVA <40 or >78 ETDRS letters (n=6), CST >500 mm (n=1), or both BCVA <40 or >78 ETDRS letters and CST >500 mm (n=1). BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; CST, Central Subfield Thickness.
Data cutoff date, January 19, 2024

Rapidly Advancing Development in Large Market Ophthalmology

VECTOR DELIVERY	PRODUCT CANDIDATE	INDICATION	EPIDEMIOLOGY (PREVALENCE)	IND-ENABLING	PHASE 1	PHASE 2	PHASE 3	UPCOMING MILESTONES
OPHTHALMOLOGY **R100** **Intravitreal** 	**4D-150** Aflibercept + VEGF-C RNAi	**Wet AMD**	*~3M U.S./EUMM*	PRISM				▪ **Q3:24** Phase 3 regulatory update ▪ **H2:24** Initial interim data from Phase 2 Population Extension (N=32) ▪ **Q1:25** Initiate Phase 3 program
		Diabetic Macular Edema	*~5M U.S./EUMM*	SPECTRA				▪ **H2:24** Phase 2 initial interim data for Dose Confirmation (N=22)
	4D-175 Short Form Complement Factor H	**Geographic Atrophy**	*~2.5M U.S./EUMM*					▪ **Q2:24** IND filing ▪ **H2:24** Phase 1 initiation

THANK YOU

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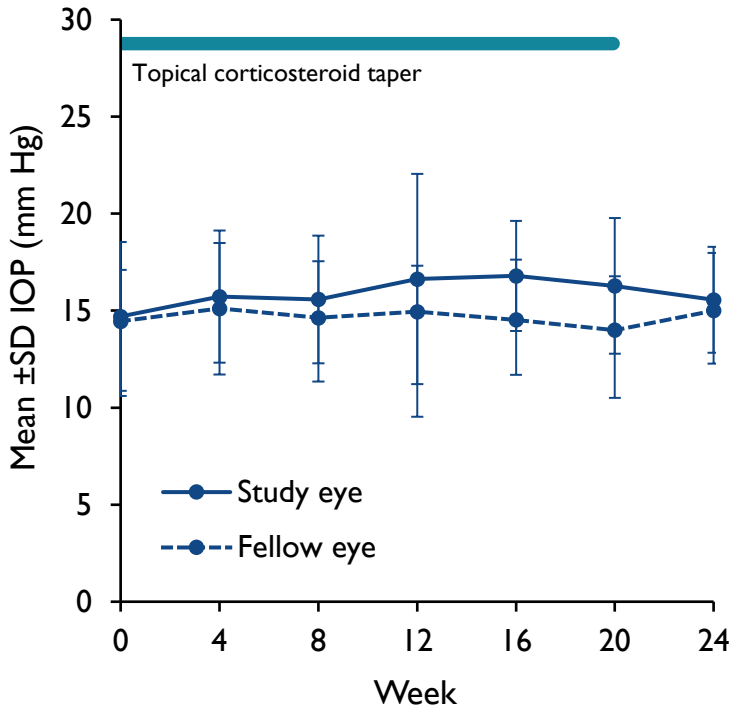
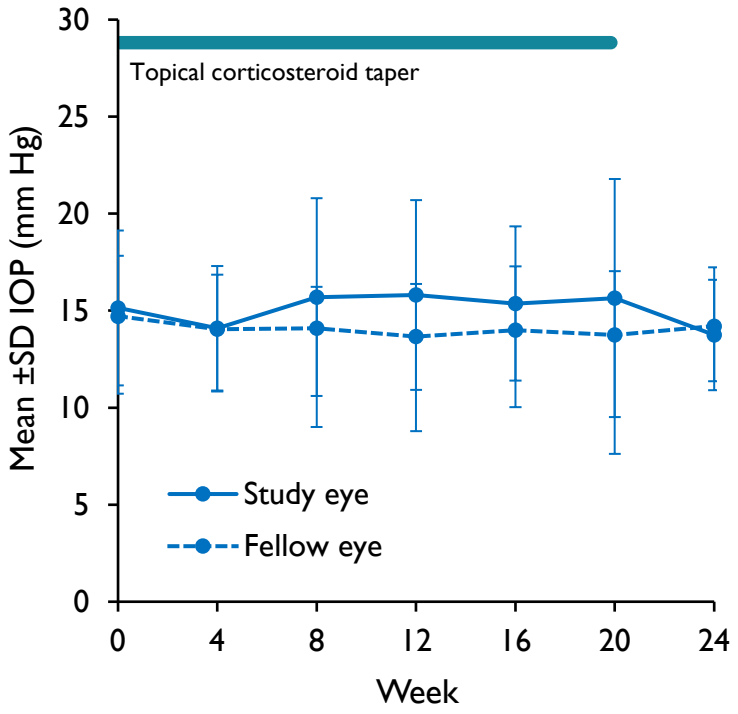
No Notable Findings on Intraocular Pressure (IOP)

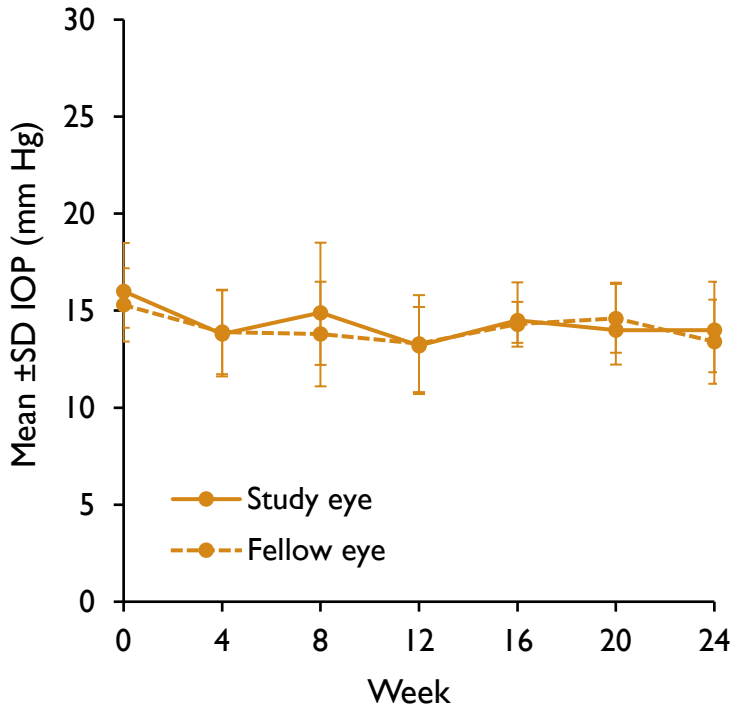
4D-150 (3E10 vg/eye)



4D-150 (1E10 vg/eye)



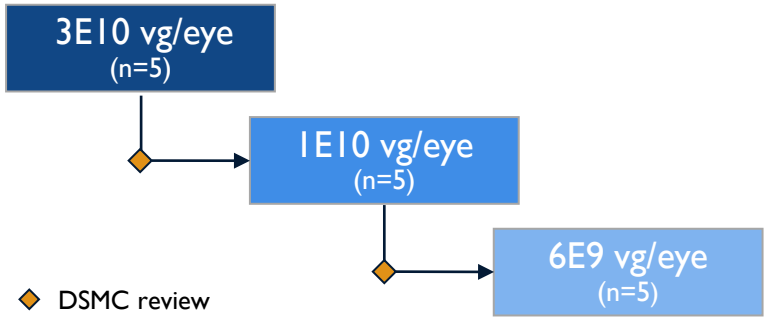
Aflibercept 2 mg Q8W



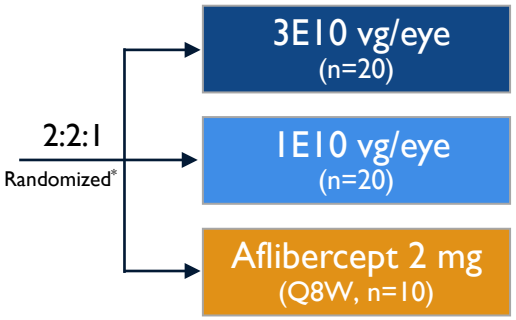
Observed data.

PRISM Phase 1/2 Clinical Trial is Evaluating 4D-150 in a Broad Range of Wet AMD Patient Populations

Dose Exploration (Phase 1)

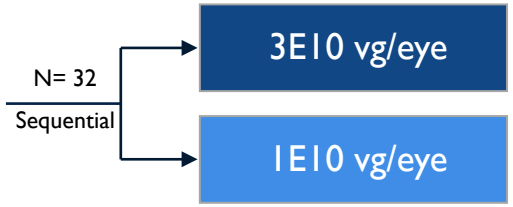


Dose Expansion (Phase 2)



Enrollment Began Jan 2023, Completed Jul 2023

Population Extension (Phase 2)



Enrollment Began Sep 2023 Completed Nov 2023

Key Inclusion Criteria

- **Anti-VEGF Injections prior 12 months:** ≥6
- **CST at Screening:** ≥300 µm OR presence of subretinal or intraretinal fluid
- **BCVA:** 25–78 ETDRS letters (20/320-20/32)

Key Inclusion Criteria

- **Anti-VEGF Injections prior 12 months:** ≥6
- **CST at Screening:** ≥325 µm AND presence of subretinal or intraretinal fluid
- **BCVA:** 34–83 ETDRS letters (20/200-20/25)

Key Inclusion Criteria

- **Anti-VEGF Injections prior 12 months:** 1-6, ≥1 in last 12 weeks
- **CST at Screening:** historical response to anti-VEGF by SD-OCT confirmed by reading center
- **BCVA:** 34–83 ETDRS letters (20/200-20/25)

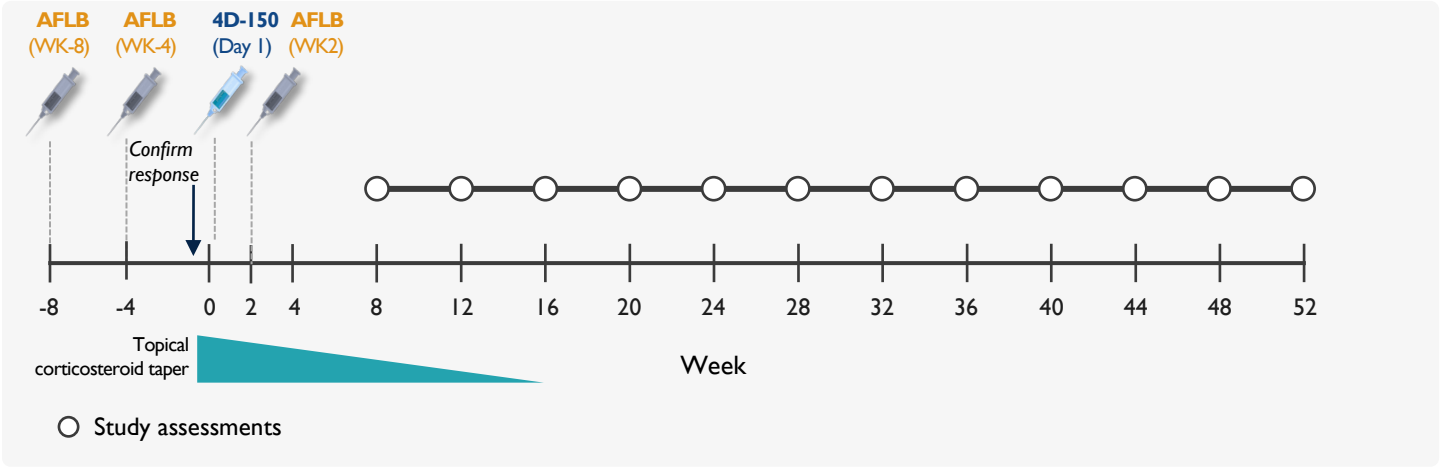
* Stratified by prior injections <9 vs. ≥9. BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

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