Interim Results from the PRISM Phase 1/2 Clinical Trial Evaluating Intravitreal 4D-150 in Adults with Neovascular Age-related Macular Degeneration

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Disclosures*

Investigator: 4DMT, Aerie/Alcon, Alexion, Allegenesis, Annexion, Aviceda, Bayer, EyeBio, EyePoint, Gemini, Genentech, Gyroscope, Ionis, Janssen, Kodiak, Kyowa Kirin, Mylan, NGM, Novartis, Ocular Therapeutix, OcuTerra, Opthea, ONL, RecensMedical, Regeneron, Regenxbio, Roche, Stealth, Unity

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Speaker: Alimera, Allergan, Amaros, Apellis, Astellas, Bayer, EyePoint, Genentech, Regeneron

Equity: Amaros, Boston Image Reading Center, Janssen, Network Eye, ReVive, US Retina

Founder: Network Eye

*Disclosures and specified roles during the last calendar year.

Key Takeaways

PRISM Phase 2 Clinical Trial Interim Results

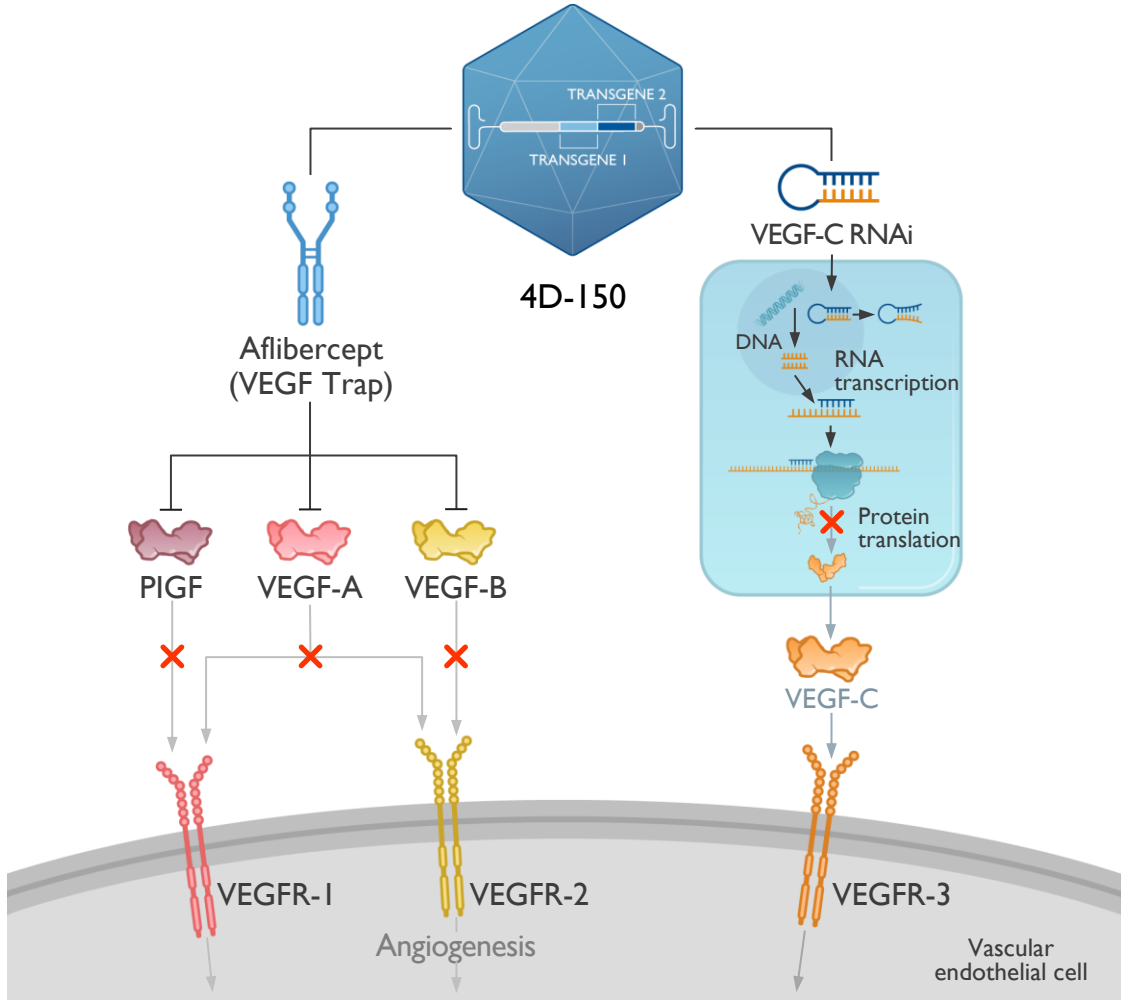
- 4D-150: dual-transgene intravitreal gene therapy
  - Evolved retinotropic AAV vector, dual-transgene payload (aflibercept, VEGF-C RNAi)
- PRISM Phase 1/2 clinical trial: Evaluation of 4D-150 in a broad wet AMD population
- PRISM Phase 2 interim results (Week 24)—3×10^{10} vg/eye:
  - 4D-150 was safe and well tolerated
    - No 4D-150–related serious adverse events and no clinically significant inflammation
    - 100% (49/49) of participants completed prophylactic corticosteroid regimen on schedule
  - Durable clinical activity observed in both Phase 2 cohorts
    - 89% reduction in annualized anti-VEGF injections
    - Stable visual acuity
    - Sustained reduction in CST, stabilization of CST fluctuations

AAV, adeno-associated virus; VEGF, vascular endothelial growth factor.

4D-150

Dual-Transgene Intravitreal Gene Therapy

- Primate-evolved intravitreal R100 capsid carrying a dual-transgene payload
  - Aflibercept and VEGF-C RNAi
- Single-dose intravitreal administration
- Widespread delivery to all major regions and layers of the macula
- Robust pan-retinal transgene expression
- Inhibition of 4 distinct VEGF family members: VEGF-A, -B, -C, and PlGF

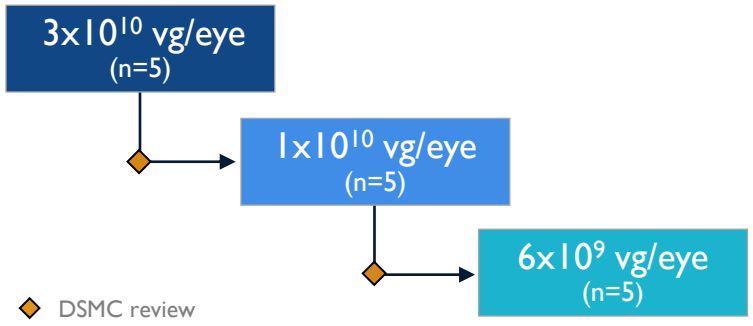


PlGF, placental growth factor; VEGF, vascular endothelial growth factor.

PRISM Phase 1/2 Clinical Trial

Evaluation of 4D-150 in a Broad Range of Wet AMD Populations

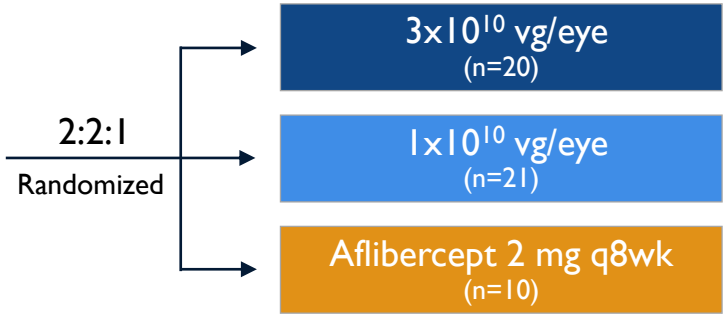
Phase 1 Dose Exploration



Key Inclusion Criteria

- Anti-VEGF injections in the prior 12 months: ≥6
- CST: ≥300 µm ***or*** presence of subretinal or intraretinal fluid
- BCVA: 25–78 ETDRS letters

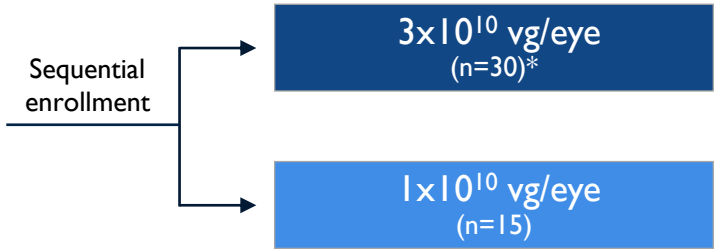
Phase 2a Dose Expansion



Key Inclusion Criteria

- Anti-VEGF injections in the prior 12 months: ≥6
- CST: ≥325 µm ***and*** presence of subretinal or intraretinal fluid
- BCVA: 34–83 ETDRS letters

Phase 2b Population Extension



Key Inclusion Criteria

- Anti-VEGF injections in the prior 12 months: 1–6 (≥1 in last 12 wks)
- CST: No minimum
- BCVA: 34–83 ETDRS letters

*Includes participants in the alternative steroid cohort who enrolled under the Population Extension eligibility criteria (n=13).

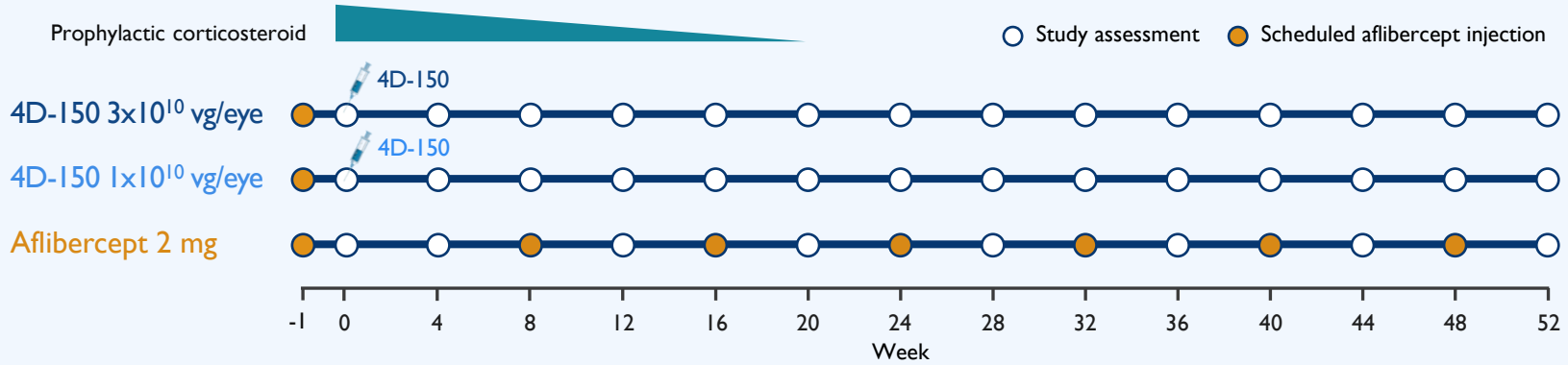
Study Design

Phase 2 Dose Expansion and Population Extension Cohorts

Phase 2a Dose Expansion

Key Eligibility Criteria

- ≥6 anti-VEGF injections during prior 12 months
- CST: ≥325 μm ***and*** presence of subretinal or intraretinal fluid
- BCVA: 34–83 ETDRS letters



Phase 2b Population Extension

Key Eligibility Criteria

- 1–6 anti-VEGF injections during prior 12 months: (≥1 injection in the last 12 weeks)
- CST: No minimum
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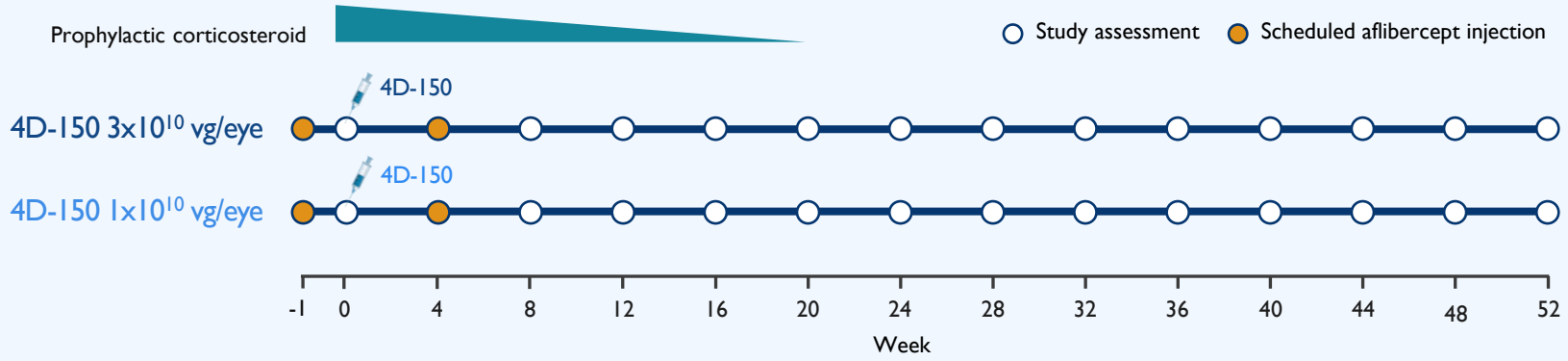


Baseline Characteristics (Phase 2)

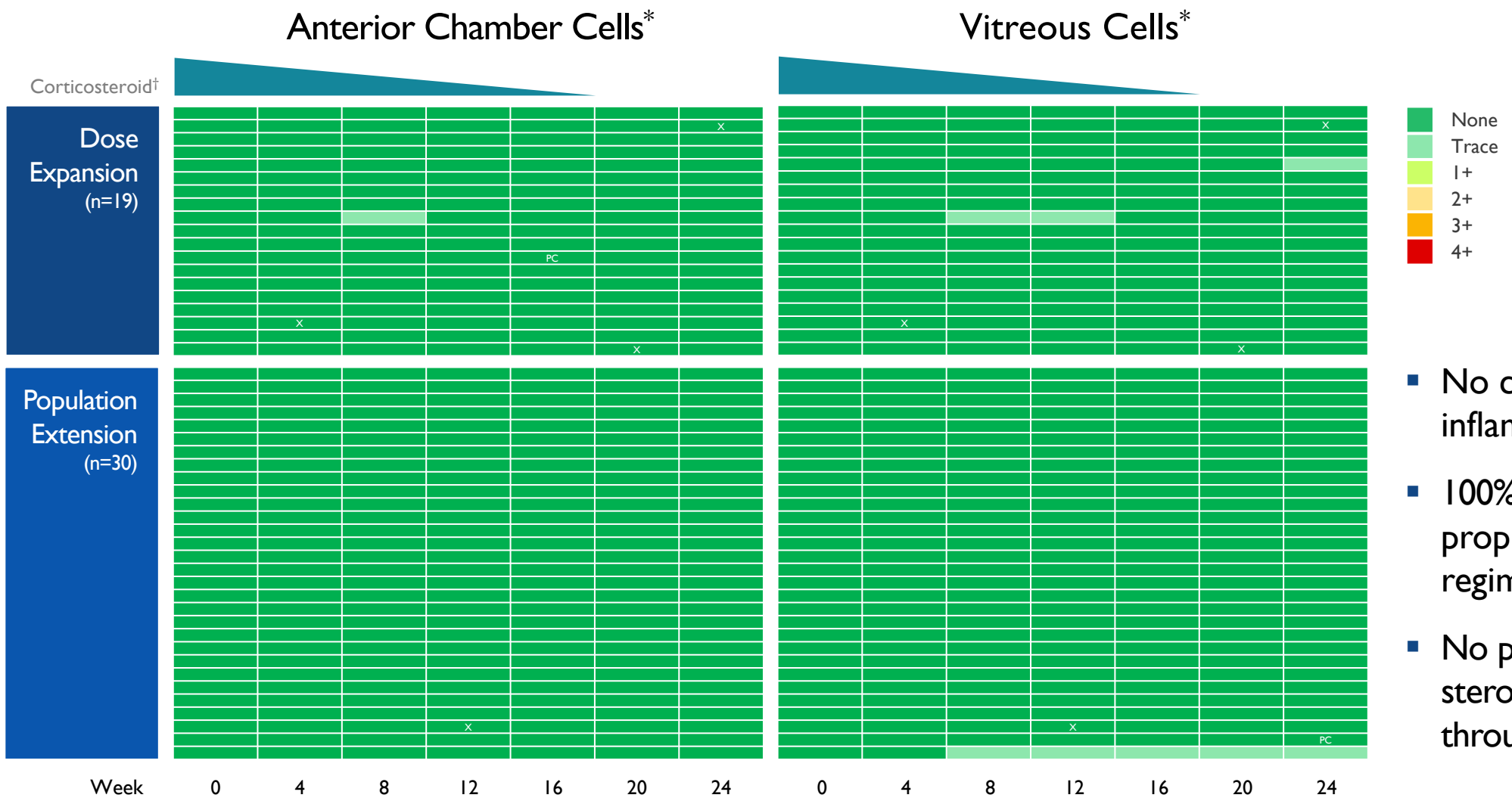
Broad Range of Disease Activity and Anti-VEGF Injection Burden

	Dose Expansion			Population Extension	
	4D-150 3×10^{10} vg/eye (N=20)	4D-150 1×10^{10} vg/eye (N=21)	Aflibercept 2 mg Q8W (N=10)	4D-150 3×10^{10} vg/eye (N=30)	4D-150 1×10^{10} vg/eye (N=15)
Mean ±SD age, years	77 ±8.0	77 ±8.6	80 ±4.1	77 ±7.7	78 ±8.6
Female, n (%)	8 (40)	11 (52)	5 (50)	20 (67)	6 (40)
Race, n (%)					
White	18 (90)	21 (100)	9 (90)	30 (100)	14 (93)
Asian	2 (10)	0	1 (10)	0	1 (7)
Mean ±SD time since diagnosis, years	4.0 ±3.0	2.9 ±2.2	1.9 ±1.5	1.8 ±3.5	0.7 ±0.9
Mean ±SD BCVA, ETDRS letters	68 ±11.3	71 ±12.4	71 ±13.2	71 ±9.9	73 ±8.8
Mean ±SD central subfield thickness, µm	429 ±89.3	465 ±114.1	419 ±64.3	336 ±135.0	314 ±70.8
Mean prior *annualized* injection rate*	10.0	9.9	9.0	8.3	10.7
Mean ±SD *actual* injections, prior 12 mo*	9.9 ±2.4	9.4 ±2.1	9.3 ±0.9	4.4 ±2.0	4.3 ±2.1

*Includes Day -7 AFLB injection. BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation.

PRISM Phase 2 Interim Results

4D-150 3×10^{10} vg/eye (Phase 3 Dose)

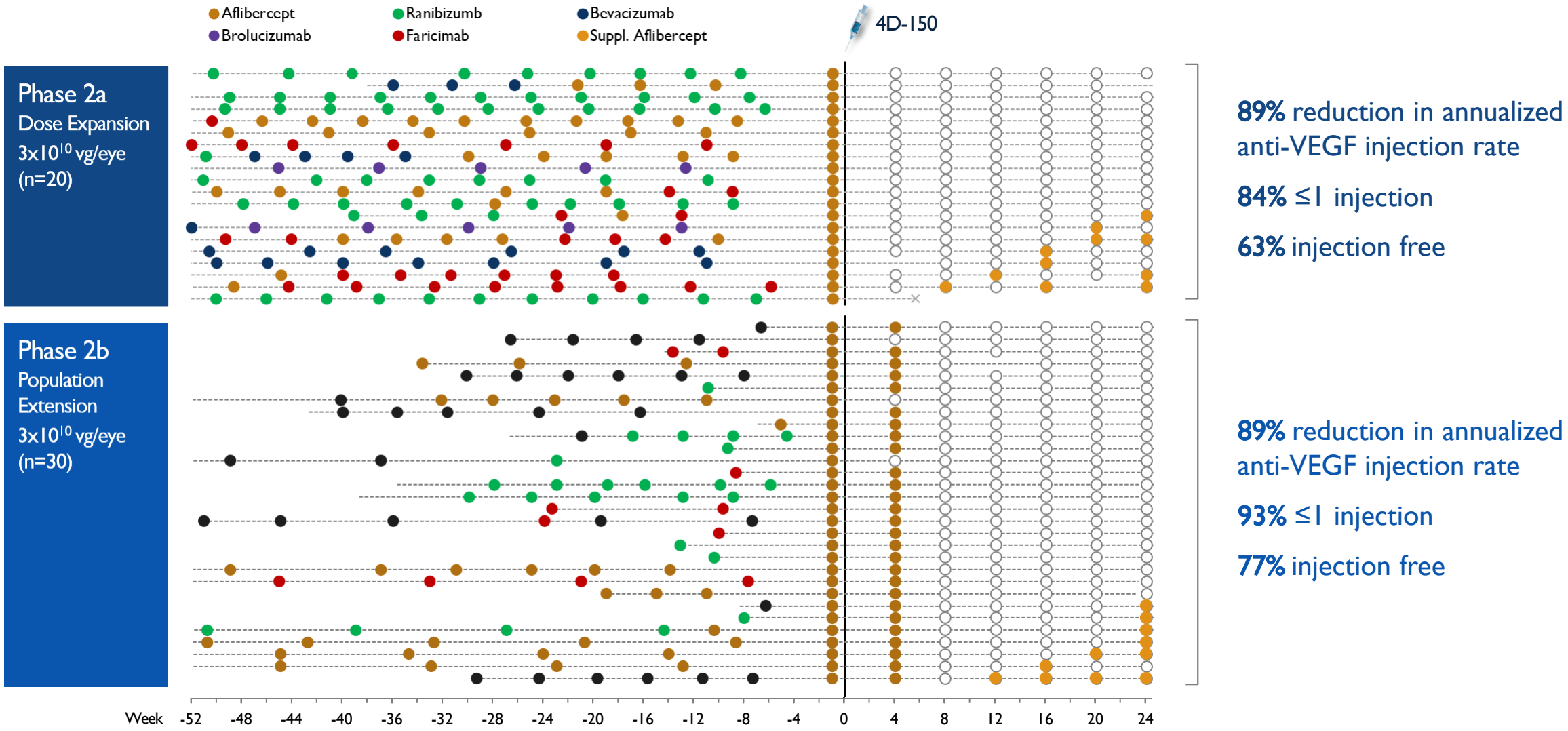


- No clinically significant inflammation
- 100% (49/49) completed prophylactic steroid regimen on schedule
- No participant restarted steroids during follow up through 24 weeks

*SUN and NEI Scores for white blood cells. †Either difluprednate ophthalmic emulsion, triamcinolone acetonide with prednisolone taper, or dexamethasone. NEI, National Eye Institute; PC, pigmented cells; SUN, Standardization of Uveitis Nomenclature; X=missed visit.

Anti-VEGF Injections (Week 24)

4D-150 3×10^{10} vg/eye: 89% Reduction in Annualized Anti-VEGF Injection Rate



89% reduction in annualized anti-VEGF injection rate

84% ≤1 injection

63% injection free

89% reduction in annualized anti-VEGF injection rate

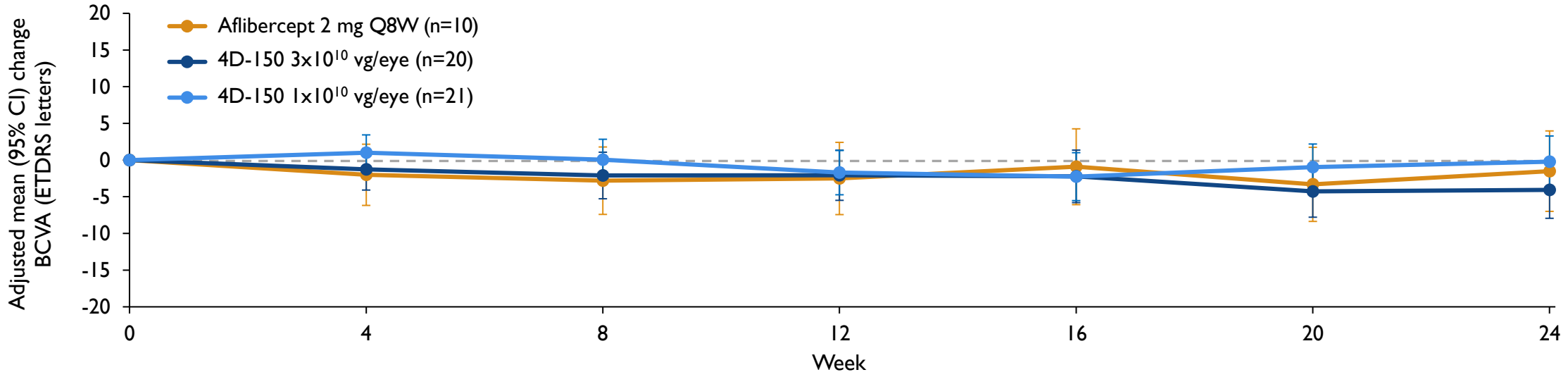
93% ≤1 injection

77% injection free

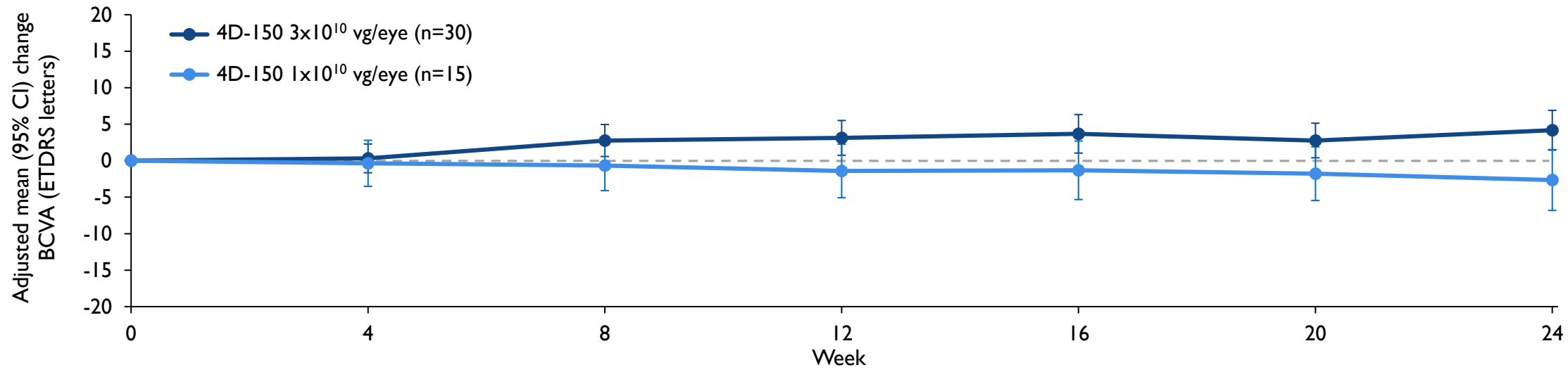
Best Corrected Visual Acuity (BCVA)

4D-150 3×10^{10} vg/eye: Stable Visual Acuity Through Week 24

Dose Expansion



Population Extension

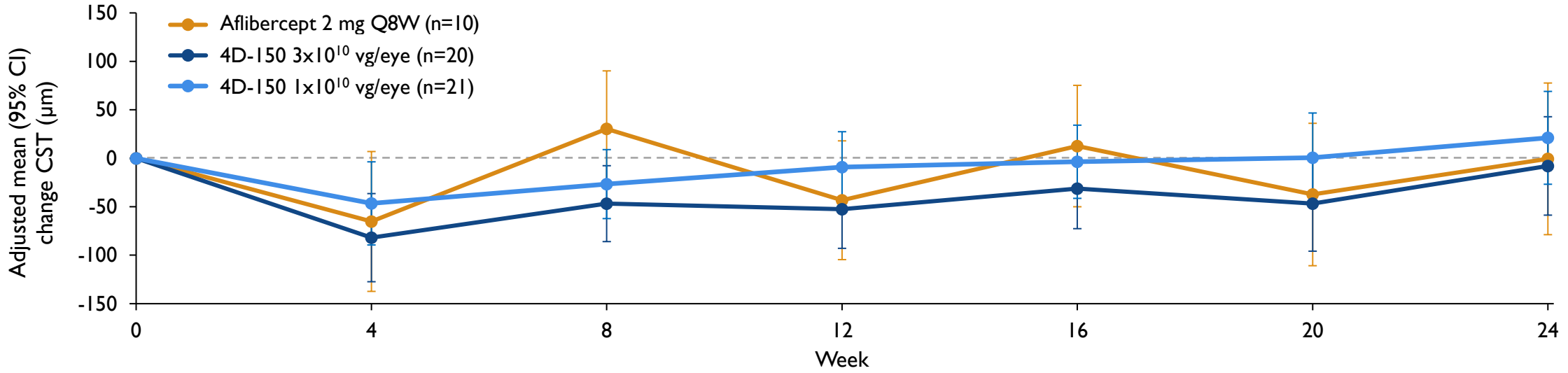


Adjusted mean (95% CI) estimated from a mixed–effect model for repeated measures including observed data (weeks 4–24) without imputing missing values. CI, confidence interval.

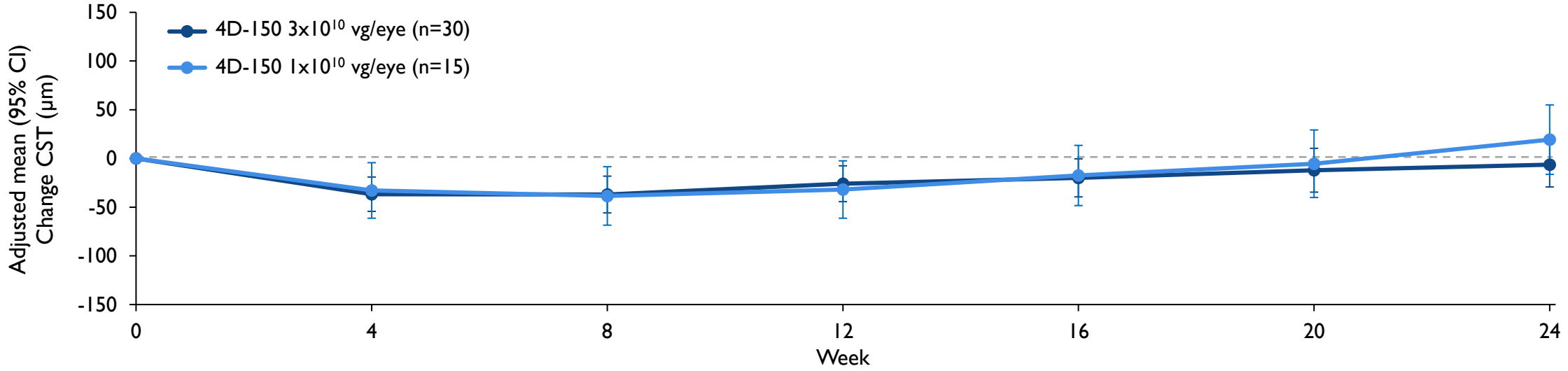
Central Subfield Thickness (CST)

4D-150 3×10[10] vg/eye: Stable Anatomic Control Through Week 24

Dose Expansion



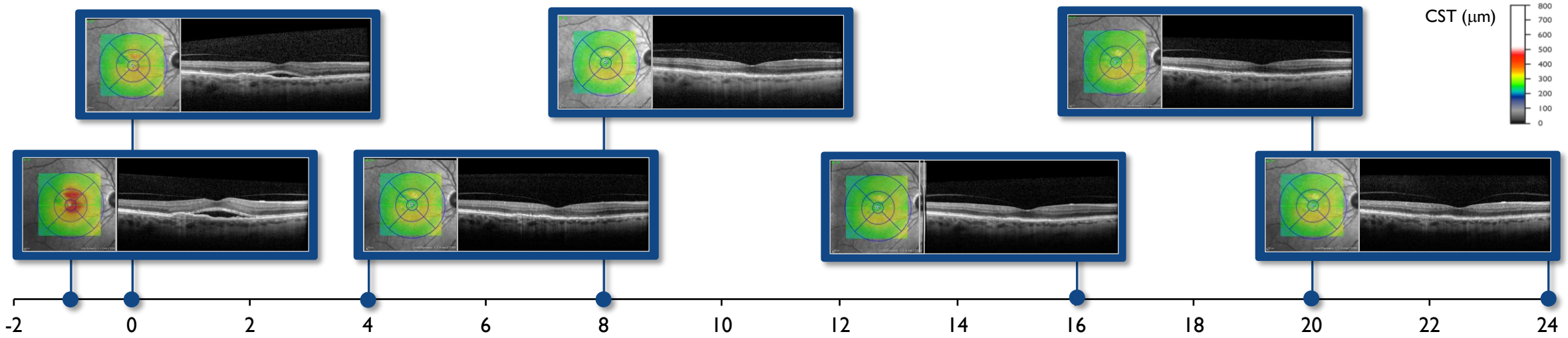
Population Extension

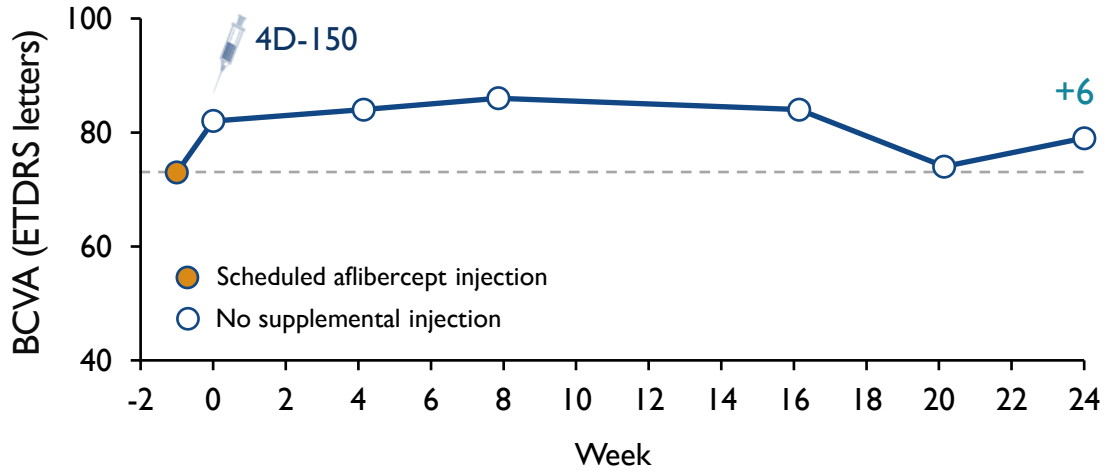


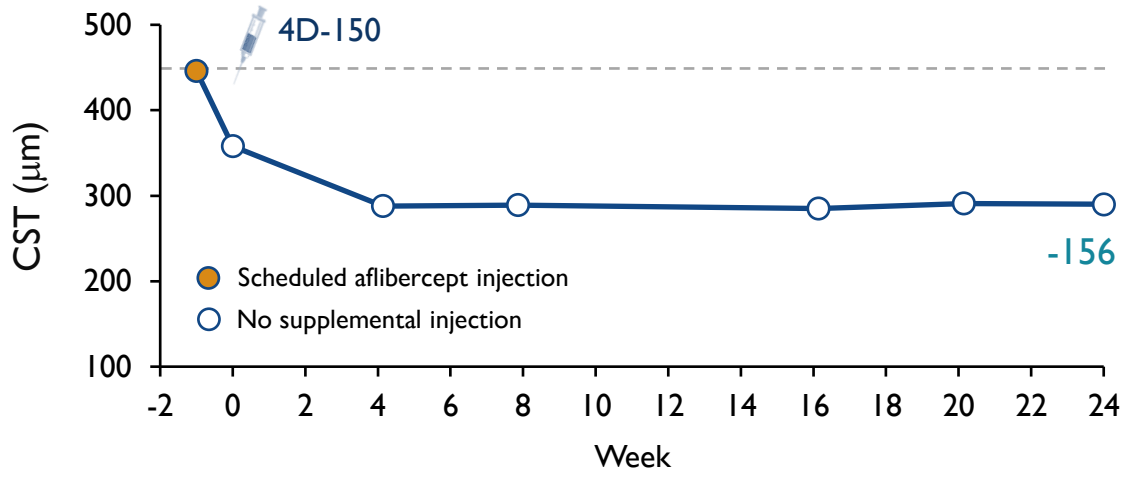
Adjusted mean (95% CI) estimated from a mixed–effect model for repeated measures including observed data (weeks 4–24) without imputing missing values. CI, confidence interval.

Case Study

Population Extension (4D-150 3×10^{10} vg/eye): 4 Anti-VEGF Injections in Prior 6 Months







Summary and Conclusions

- PRISM Phase 1/2 clinical trial
  - Broad wet AMD population with a wide range of disease activity and anti-VEGF treatment burden
- Phase 2 interim results (Week 24)—3×10^{10} vg/eye:
  - 4D-150 was safe and well tolerated
    - No 4D-150–related serious adverse events and no clinically significant inflammation
    - No hypotony, endophthalmitis, retinal vasculitis, choroidal effusions, or retinal artery occlusions
    - 100% (49/49) of participants completed prophylactic corticosteroid regimen on schedule
  - Durable clinical activity observed in both Phase 2 cohorts
    - 89% reduction in annualized anti-VEGF injections
    - Stable visual acuity
    - Sustained reduction in CST, stabilization of CST fluctuations
- Initiation of Phase 3 clinical trial anticipated in early 2025

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