PRISM

First Interim Results (24 weeks) for the Randomized Phase 2 Dose Expansion Stage of the PRISM Clinical Trial of 4D-150 in High Need Patients with nAMD

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Disclosures

- Consultant: AbbVie, Adverum, Alcon, Amgen, Annexin, Annexon, Apellis Pharmaceuticals, Aviceda Therapeutics, Beacon Therapeutics Clearside Biomedical, Complement Therapeutics, 4DMT, Exegenesis, EyePoint Pharmaceuticals, Fronterra Therapeutics, Genentech, Gyroscope Therapeutics, i-Lumen Scientific, Iveric Bio, Janssen Pharmaceuticals, Kodiak Sciences, Kriya Therapeutics, Nanoscope, Novartis, Ocular Therapeutix, Oculis, Ocuphire, OcuTerra, Olive BioPharma, Opthea, Oxular, Oxurion, Perfuse, Ray Therapeutics, Recens Medical, Regeneron Pharmaceuticals, Regenxbio, Revive, RevOpsis, Roche, Sanofi, Stealth BioTherapeutics, Thea Pharma, Unity Biotechnology, Vanotech and Vial
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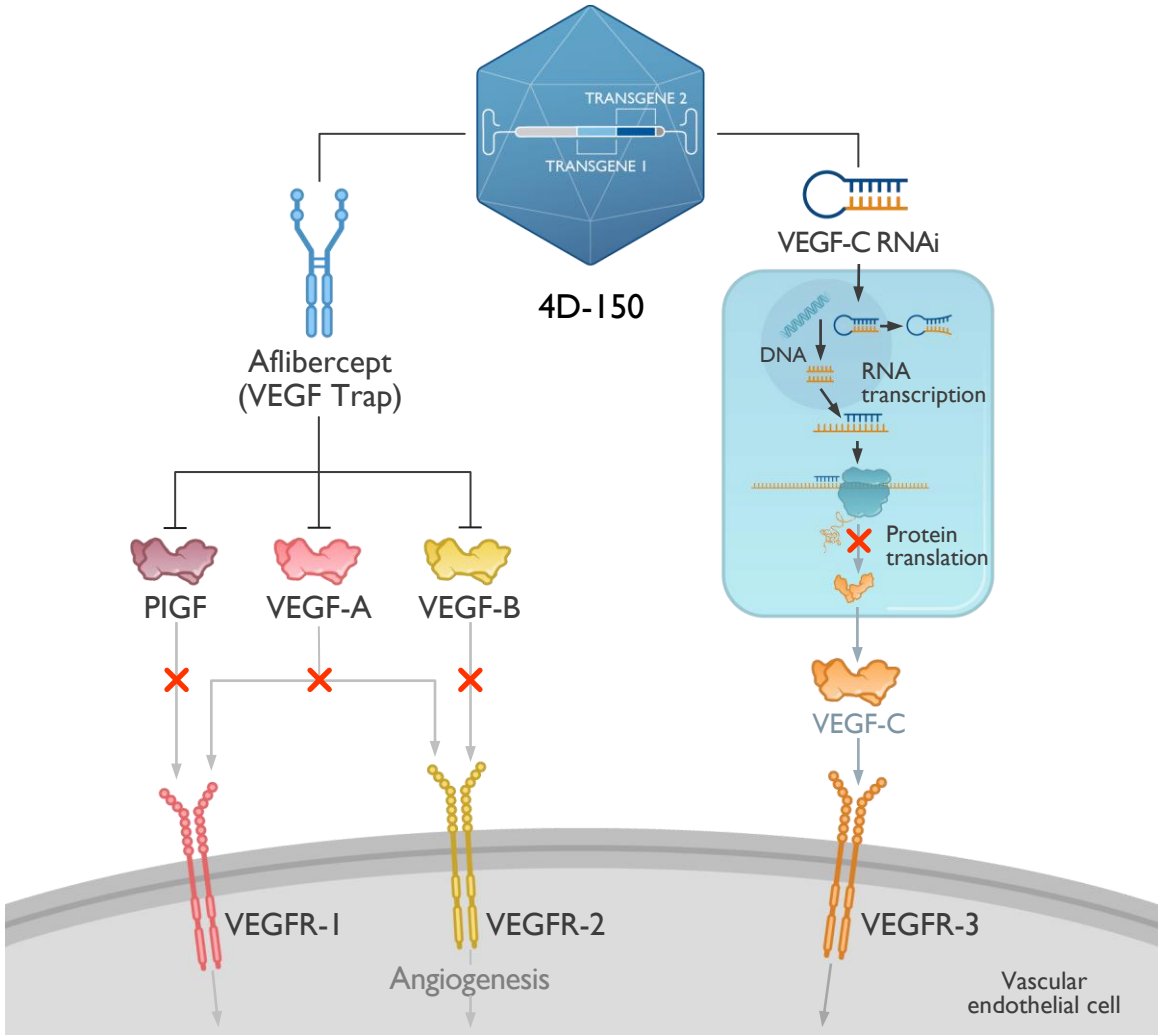
4D-150

Dual-Transgene Intravitreal Gene Therapy

- Primate-evolved intravitreal R100 capsid carrying a dual-transgene payload
  - Aflibercept & 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

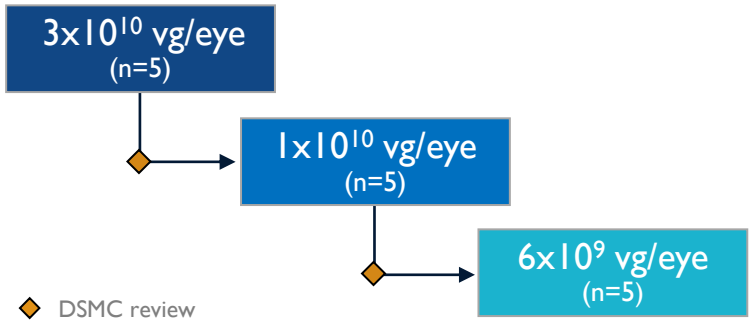


PlGF, placental growth factor; VEGF, vascular endothelial growth factor.

PRISM Clinical Trial: Phase 1 Followed By Two Phase 2 Cohorts

Evaluation of 4D-150 in Broad Range of Wet AMD Populations, Including the Most Severely Affected

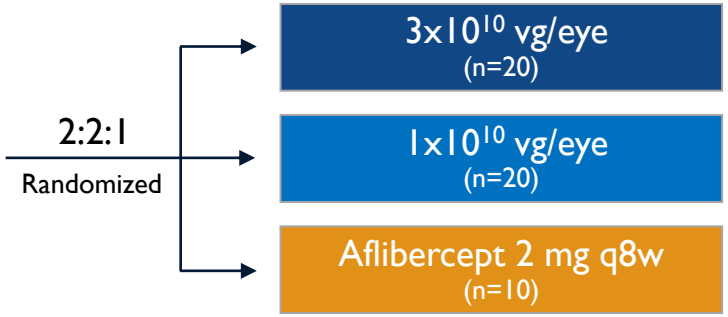
Phase 1 Dose Exploration



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 (Snellen: 20/320–20/32)

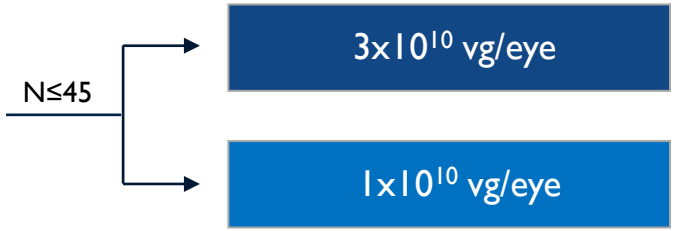
Phase 2 Dose Expansion



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 (Snellen: 20/200–20/25)

Phase 2 Population Extension



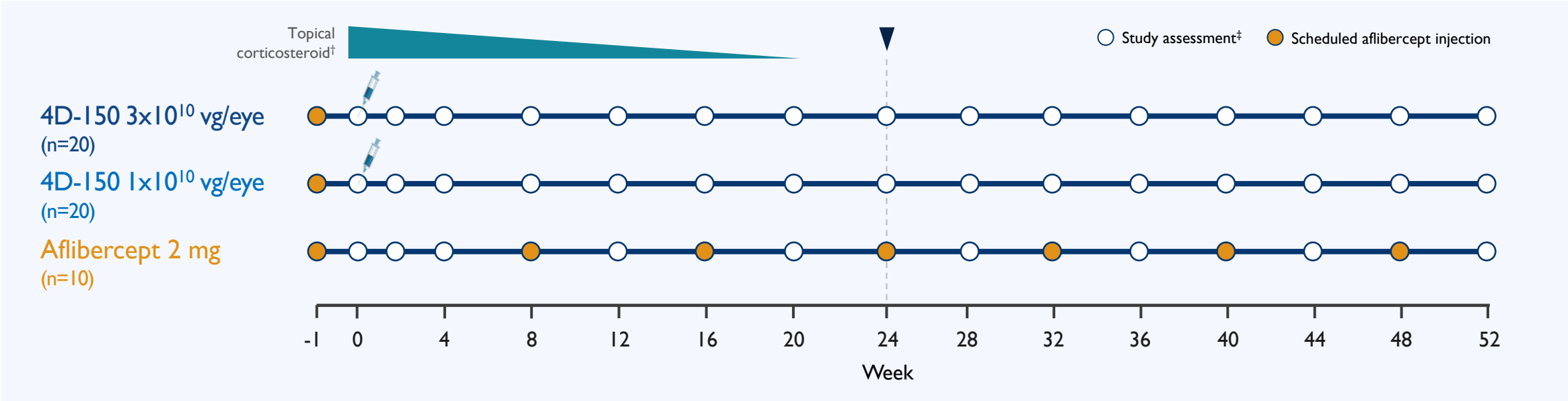
Key Inclusion Criteria

- Anti-VEGF injections in the prior 12 months: 1–6 (≥1 in last 12 wks)
- CST: Presence of subretinal or intraretinal fluid
- BCVA: 34–83 ETDRS letters (Snellen: 20/200–20/25)

Study Design

Randomized, Masked Phase 2 Clinical Trial Evaluating 4D-150 Versus Aflibercept Control*

Phase 2 Dose Expansion



Supplemental Injection Criteria

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

Key Endpoints

- Safety and tolerability
- Annualized anti-VEGF injection rate
- % participants requiring supplemental aflibercept
- Change from baseline in BCVA and CST

*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

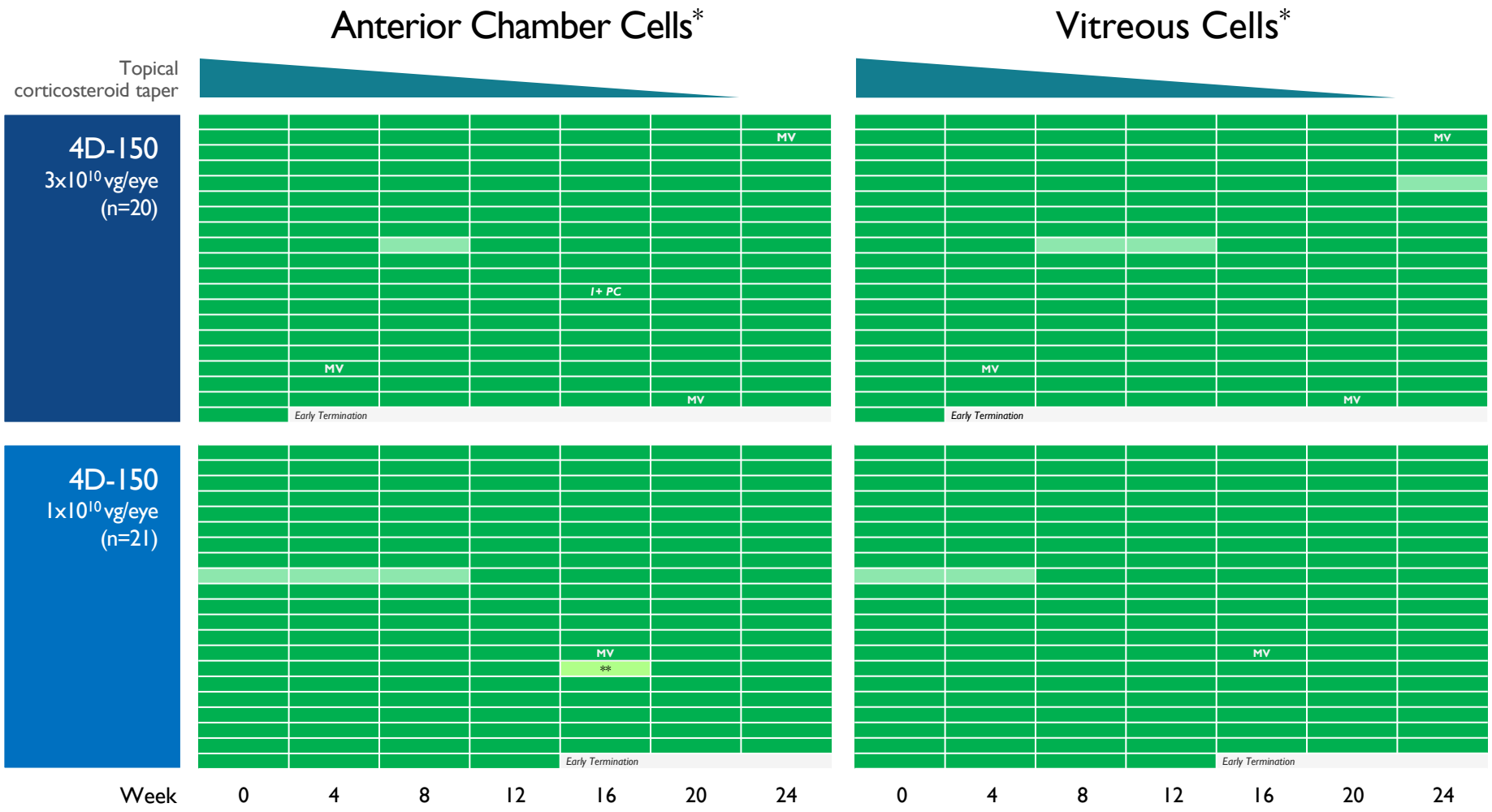
Severe Disease Activity (CST) and High Treatment Burden (Injections During Prior 12 Months)

	$3x10^{10}$ vg/eye (N=20)	$1x10^{10}$ vg/eye (N=21)	Aflibercept 2 mg (N=10)	Total (N=51)
Mean ±SD age, years	77 ±8.0	77 ±8.6	80 ±4.1	77 ±7.7
Female, n (%)	8 (40)	11 (52)	5 (50)	24 (47)
Race, n (%)				
White	18 (90)	21 (100)	9 (90)	48 (94)
Asian	2 (10)	0	1 (10)	3 (6)
Mean ±SD time since diagnosis, years	4.0 ±3.0	2.9 ±2.2	1.9 ±1.5	3.1 ±2.5
Mean ±SD BCVA, ETDRS letters	68 ±11.3	71 ±12.4	71 ±13.2	70 ±11.9
Mean ±SD central subfield thickness, μm	429 ±89.3	465 ±114.1	419 ±64.3	442 ±96.9
Mean prior *annualized* injection rate*	10.0	9.9	9.0	9.8
Mean ±SD *actual* injections in prior 12 mo*	9.9 ±2.4	9.4 ±2.1	9.3 ±0.9	9.6 ±2.0

Data cutoff date, 19 Jan 2024. *Includes Day -7 AFLB injection. BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation.

Ophthalmic Examination

No Clinically Significant or Recurrent Intraocular Inflammation*

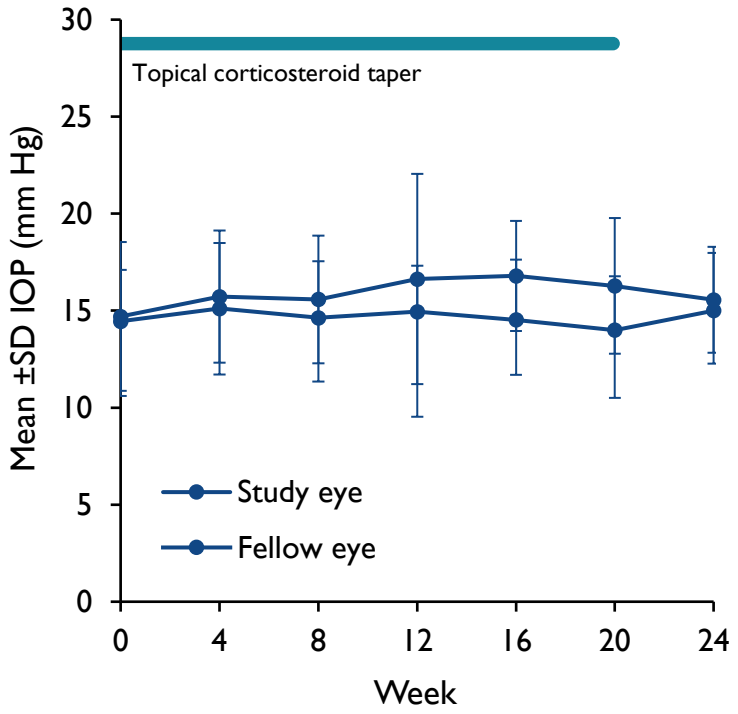


- 97% (38 of 39) completed 20-week corticosteroid taper on schedule
  - Single participant** had an increase in topical corticosteroid, completed taper by week 26
- No patients restarted steroids during follow-up for up to 48 weeks

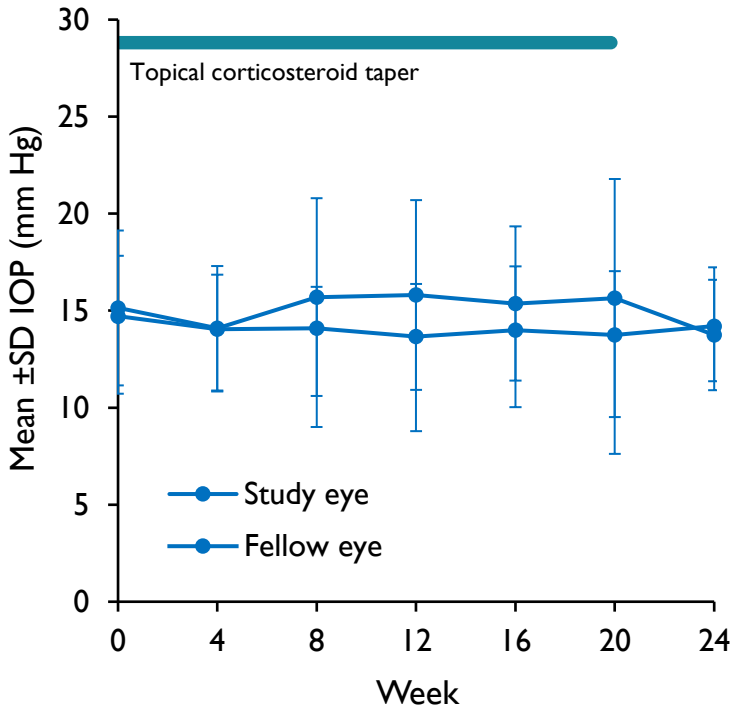
*SUN and NEI Scores for white blood cells. **Mixed WBC and pigmented cells; managed with temporary increase in topical corticosteroid dose (taper completed by Week 26).
MV, missed visit. NEI, National Eye Institute; SUN, Standardization of Uveitis Nomenclature. Dark grey bars indicate early termination (unrelated to study treatment).

Intraocular Pressure (IOP)

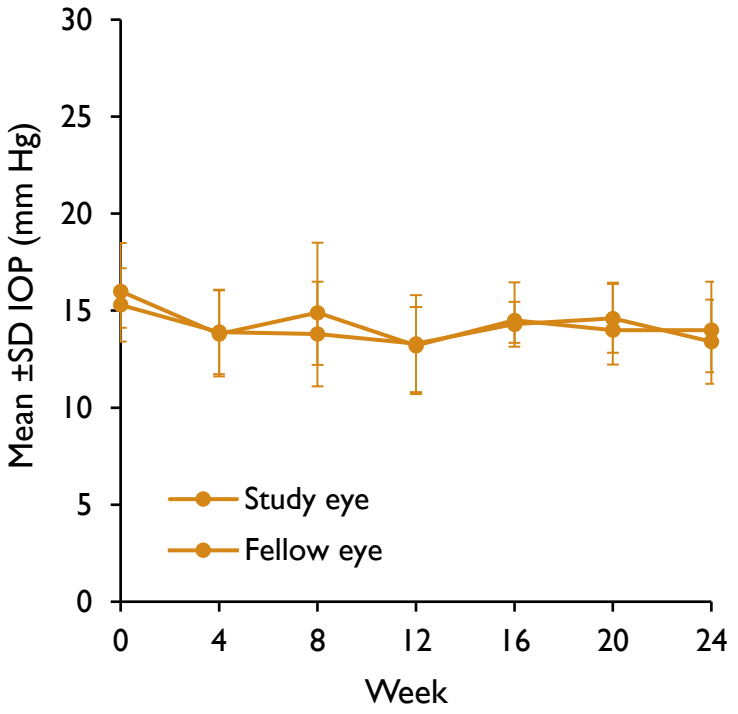
4D-150 ($3x10^{10}$ vg/eye)



4D-150 ($1x10^{10}$ vg/eye)



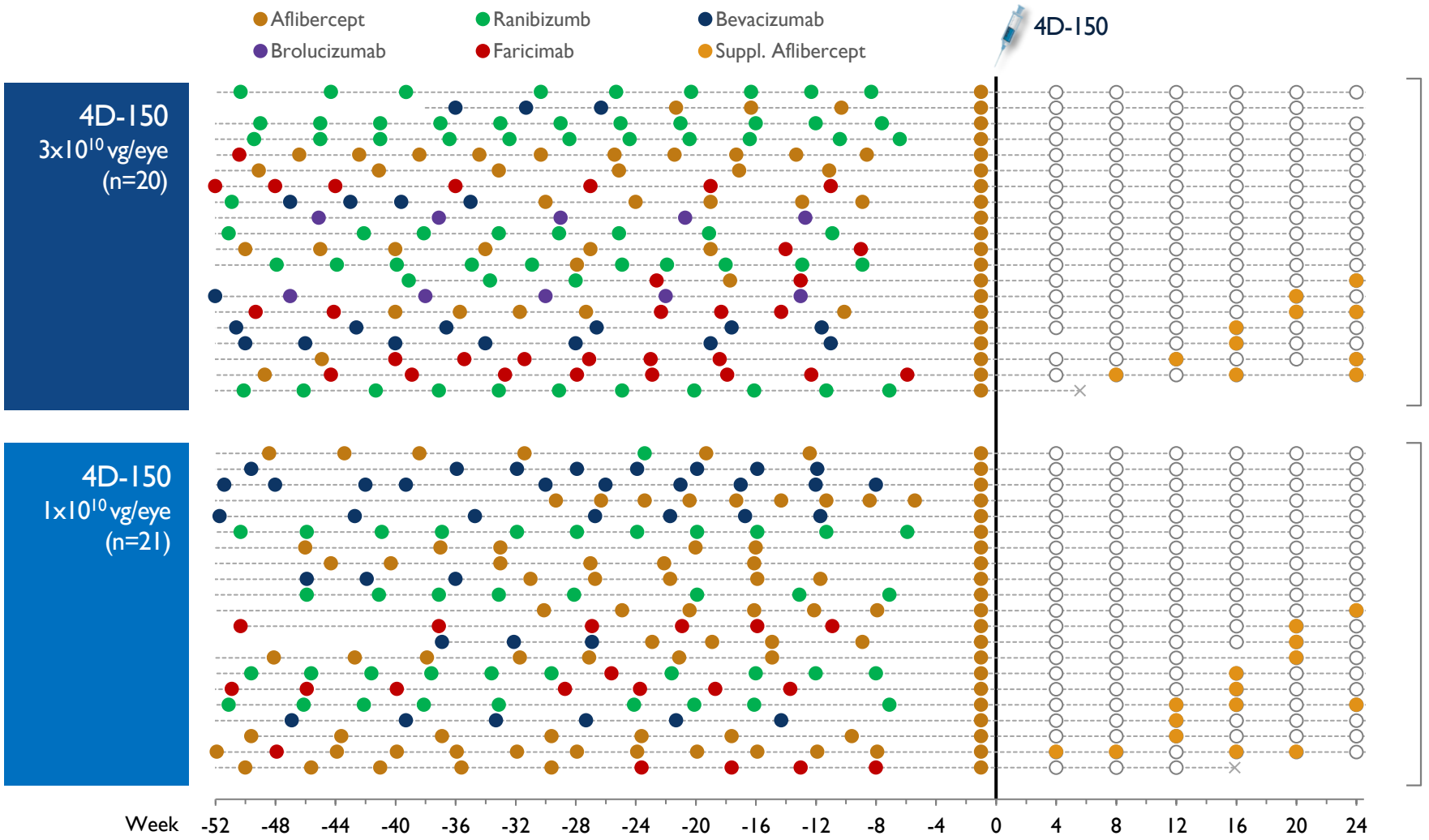
Aflibercept 2 mg Q8W



Observed data.

Anti-VEGF Injections (Week 24)

Up to 89% Reduction in Annualized Anti-VEGF Injection Rate in Highest Treatment Burden Patients



89% reduction in annualized anti-VEGF injection rate

84% 0–1 injection

63% injection-free

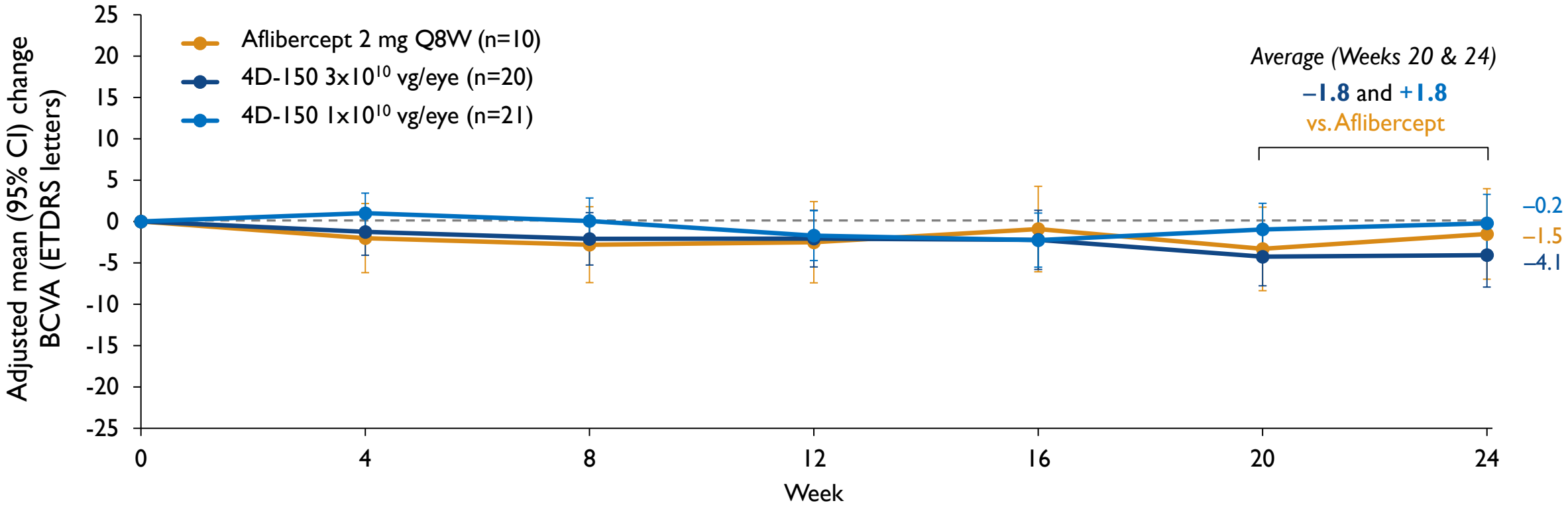
85% reduction in annualized anti-VEGF injection rate

90% 0–1 injection

50% injection-free

Best Corrected Visual Acuity

Stable Visual Acuity Through Week 24

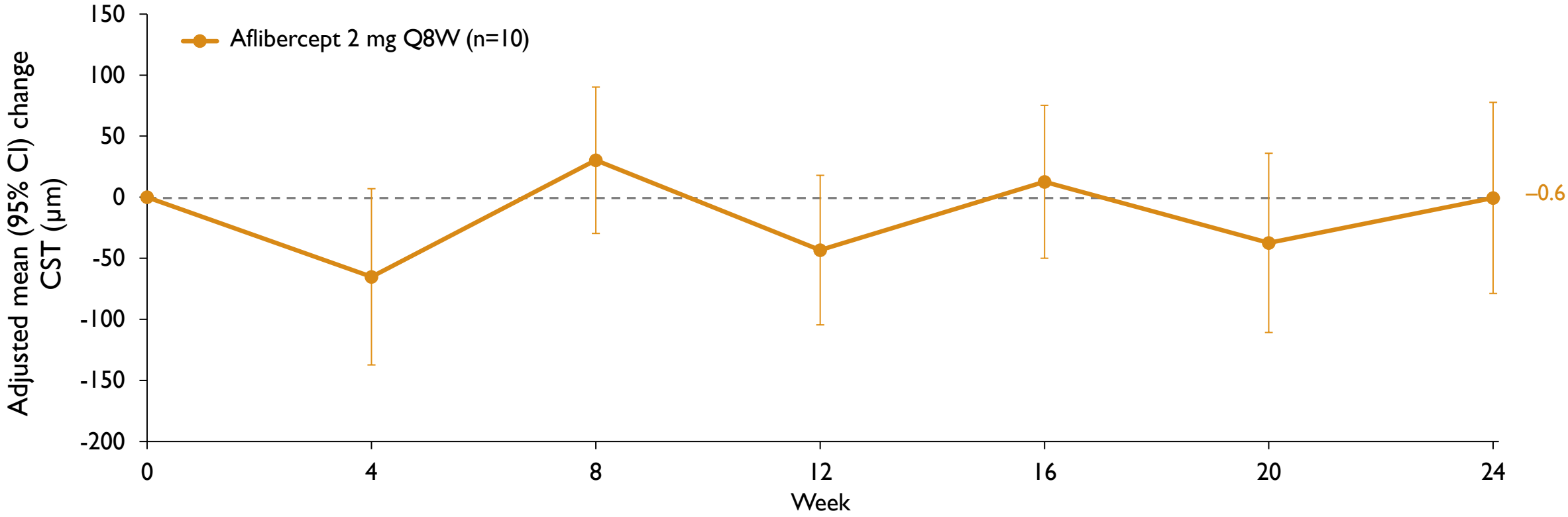


Difference (95% CI) vs Aflibercept	Week 20	Week 24
4D-150 (3x10^10 vg/eye)	–1.0 (–7.2, 5.3)	–2.6 (–9.3, 4.2)
4D-150 (1x10^10 vg/eye)	2.3 (–3.6, 8.3)	1.3 (–5.2, 7.8)

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

Central Subfield Thickness (CST)

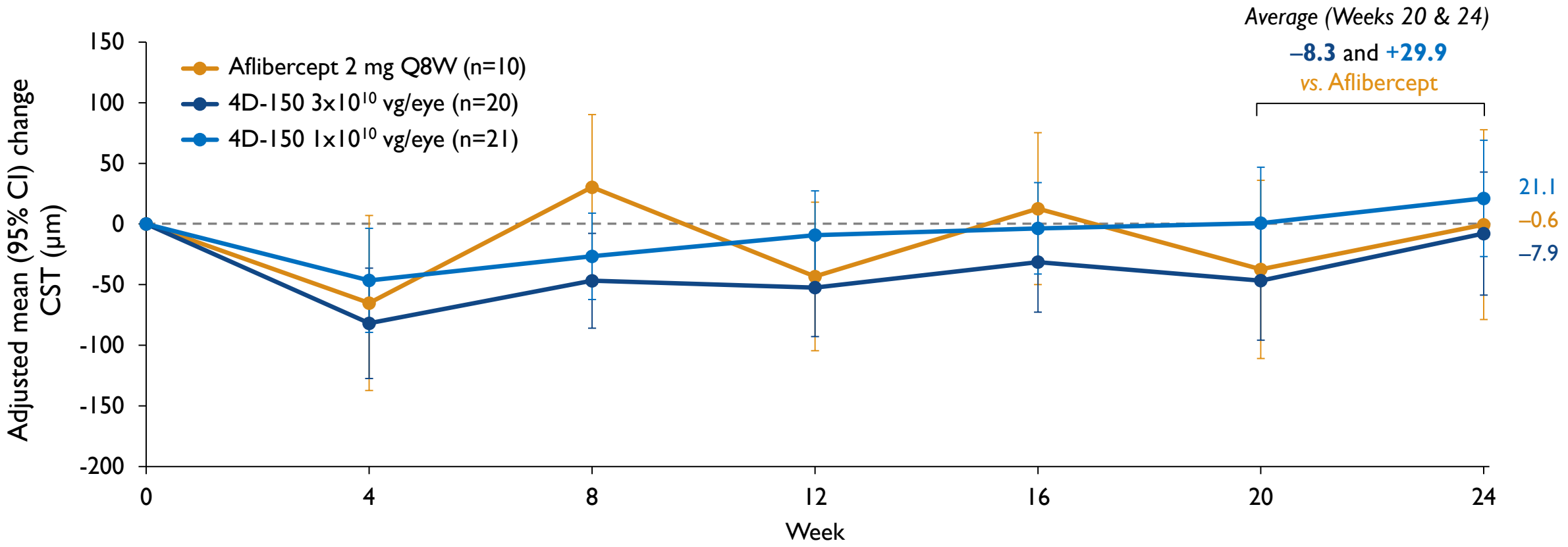
Considerable Variability Observed in Bimonthly Aflibercept Group



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. CI, confidence interval.

Central Subfield Thickness (CST)

Higher Dose 4D-150: Strong Anatomic Control



Difference (95% CI) vs Aflibercept	Week 20	Week 24
4D-150 (3x10[10] vg/eye)	–9.3 (–97.9, 79.3)	–7.3 (–101, 86.2)
4D-150 (1x10[10] vg/eye)	38.1 (–48.9, 125.2)	21.7 (–70.4, 113.8)

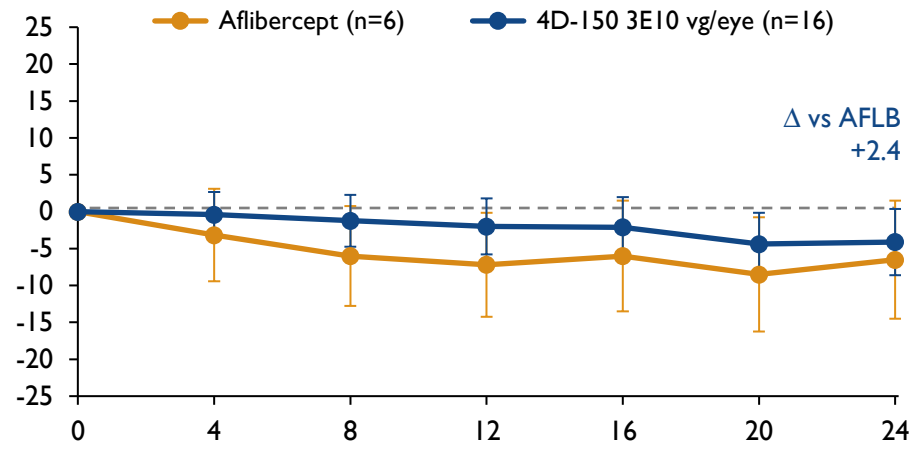
Baseline=Day -7. Adjusted mean, difference in adjusted mean and 95% CI estimated from a mixed–effect model for repeated measures including observed data (weeks 4-24) without imputing missing values. CI, confidence interval.

4D-150 High Dose:
Vision and CST Results for Potential Phase 3 Eligible Patient Population*

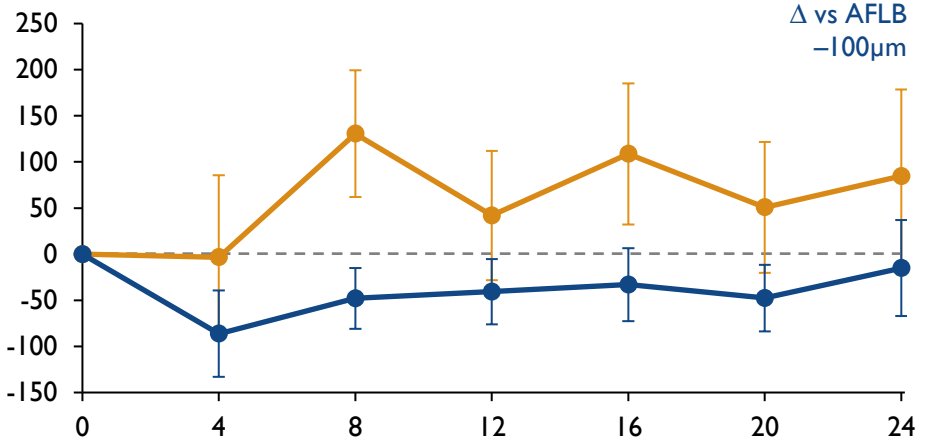
Preliminary Phase 3 Eligibility Criteria:

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

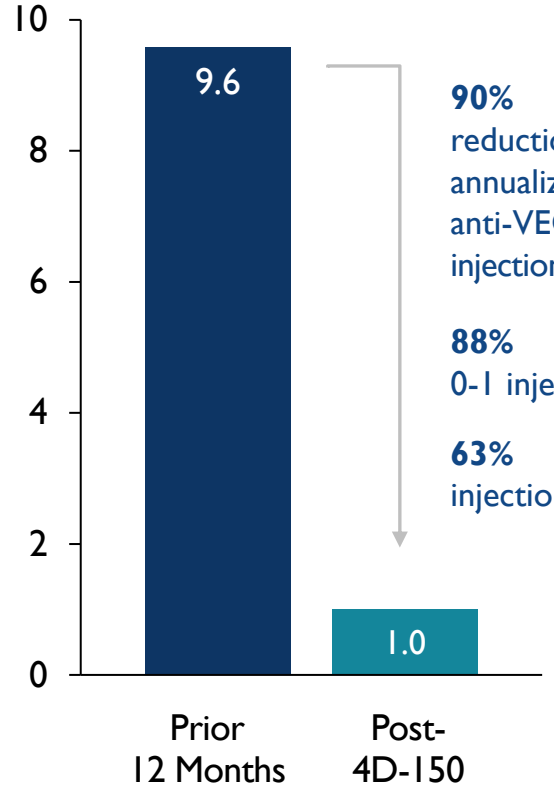
Adjusted mean ±95% CI change in BCVA (ETDRS letters)



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



Anti-VEGF Injections



90% reduction in annualized anti-VEGF injection rate

88% 0-1 injections

63% injection-free

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.
*Participants excluded based on BCVA <40 or >78 ETDRS letters (n=6), CST >500 µm (n=1), or both BCVA <40 or >78 ETDRS letters and CST >500 µm (n=1). BCVA, best corrected visual acuity; CI, confidence interval; CST, central subfield thickness.

Conclusions

- 4D-150 was safe and well tolerated through Week 24 in individuals with severe disease activity and high anti-VEGF treatment burden:
  - No 4D-150–related SAEs
  - No clinically significant or recurrent intraocular inflammation
  - No patients restarted steroids, through up to 48 weeks of follow-up
  - No hypotony, endophthalmitis, retinal vasculitis, choroidal effusions, or retinal artery occlusions
- Stable visual acuity observed through Week 24 in both 4D-150 dose groups
- 4D-150 $3x10^{10}$ vg/eye:
  - 89% reduction in mean annualized anti-VEGF injection rate
  - 84% 0–1 injections; 63% supplemental injection-free
  - Sustained reduction in CST, stabilization of CST fluctuations
- Expect to initiate Phase 3 program in Q1 2025

CST, central subfield thickness; SAE, serious adverse event.

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