A Phase 1/2 Clinical Trial Evaluating 4D-150, a Dual-transgene Intravitreal Gene Therapy in Patients with Wet Age-Related Macular Degeneration: Interim Results

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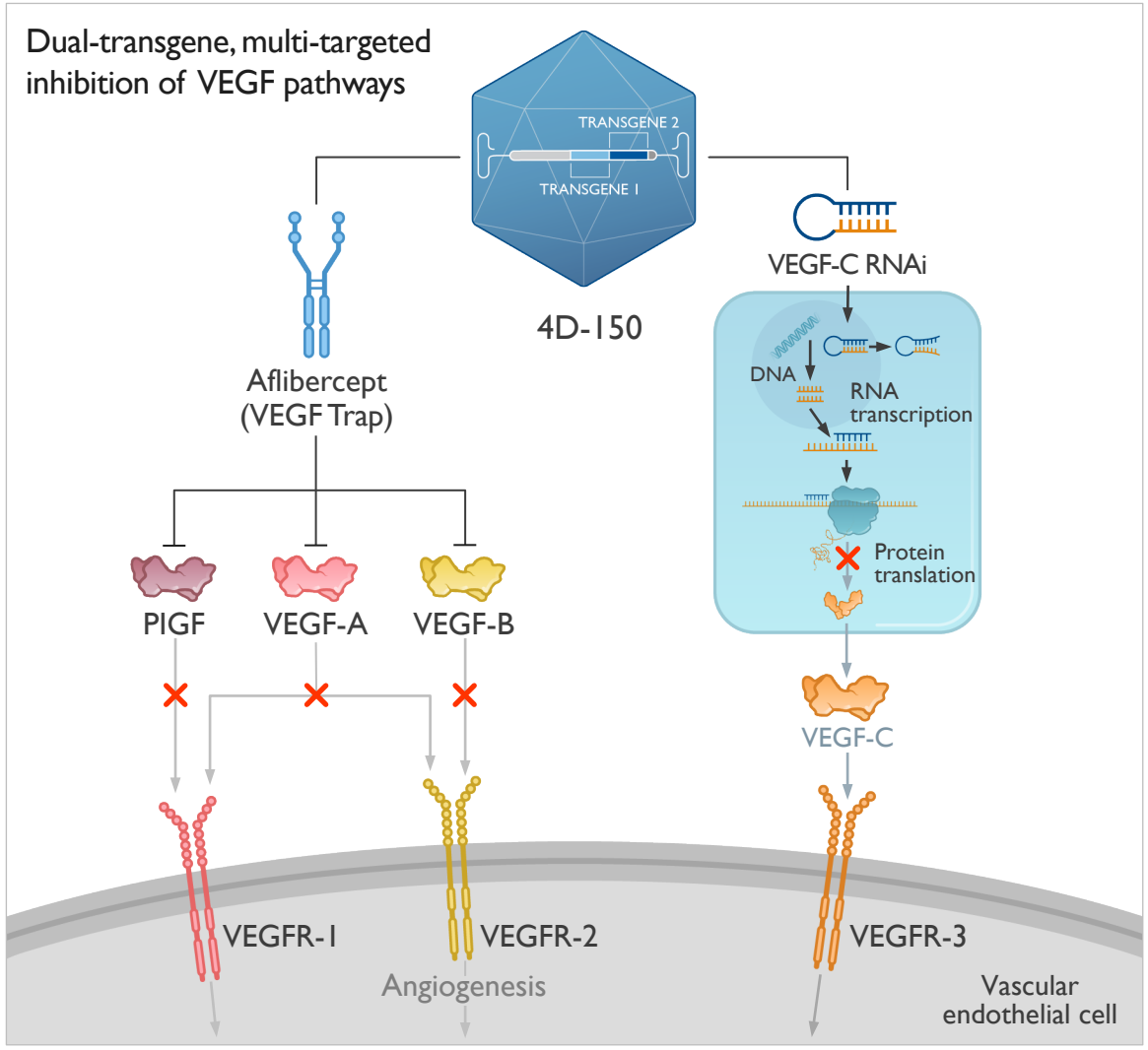
Disclosures

- **Consultant:** Abbvie, Adverum Biotechnologies, Aerie Pharmaceuticals, AGTC, Aldebaran Therapeutics, Allergan, Apellis Pharmaceuticals, Arrowhead, Pharmaceuticals, Aviceda Therapeutics, Bausch & Lomb, BroadWing Bio, Clearside, 4D Molecular Therapeutics, Exgenesis, Eyepoint Pharmaceuticals, Fronterra Therapeutics, Genentech, Gyroscope Therapeutics, i-Lumen scientific, Iveric Bio, Janssen Pharmaceuticals, Kato Pharmaceuticals, Kartos Therapeutics, Kodiak Sciences, Kriya Therapeutics, Ocular Therapeutix, Oculis, Ocuterra, Olives Bio, Opthea, Oxurion, Nanoscope, Notal, Novartis, Perfuse, PolyPhotonix, Protagonist, Ray Therapeutics, Recens Medical, Regeneron Pharmaceuticals, Regenxbio, Roche, Revopsis, Stealth Biotherapeutics Therapeutics, Thea Pharma, Unity Biotechnology, Vanotech, Vial
- **Research Support:** Adverum Biotechnologies, Annexon Biosciences, Apellis Pharmaceuticals, 4D Molecular Therapeutics, Genentech, Gyroscope Therapeutics, Iveric Bio, Kodiak, Neurotech, NGM Biopharmaceuticals, Novartis, Ocular Therapeutix, Oculis, Ocuterra, Opthea, Oxurion, Regenxbio, Roche, Unity Biotechnology
- **Equity:** Aviceda Therapeutics, PolyPhotonix, Recens Medical, Revopsis, Oculis, Vial

4D-150: Overview

- Primate-evolved retinotropic 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 retina
- Efficient transduction of retinal cells
- Robust pan-retinal transgene expression
- Inhibition of 4 distinct VEGF family members (VEGF-A, B, C, and PlGF)

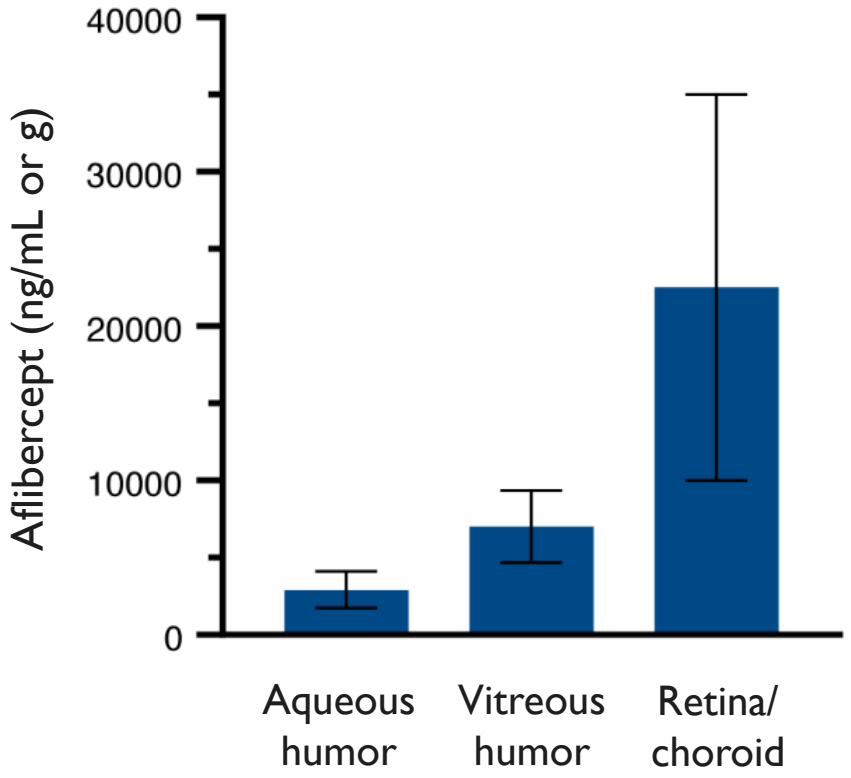


PlGF, placental growth factor; VEGF, vascular endothelial growth factor.

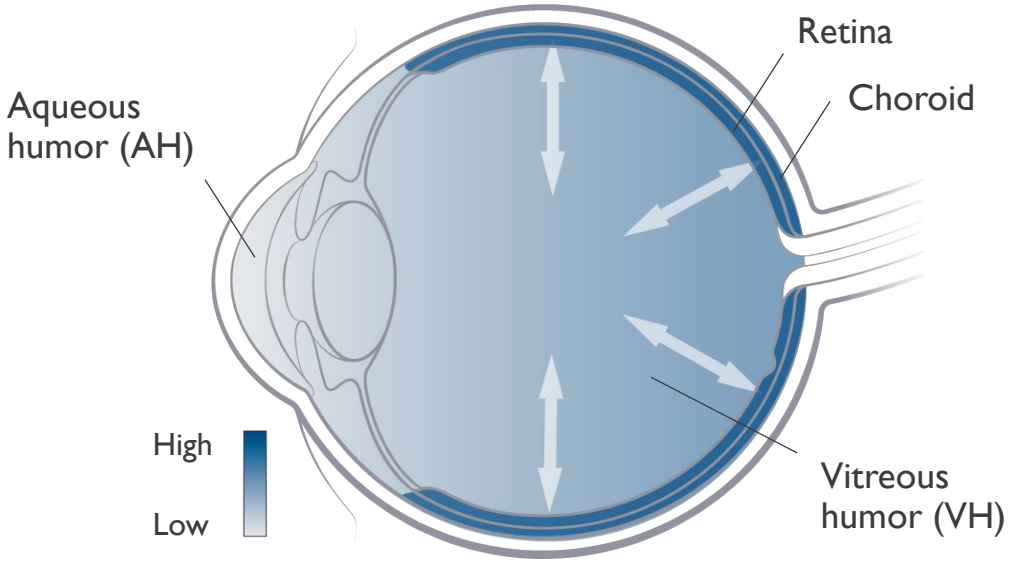
Intravitreal 4D-150 Biodistribution

RETINOTROPIC R100 VECTOR FACILITATES HIGH-LEVEL EXPRESSION WITHIN THE RETINA

Aflibercept Concentration (NHP)*



4D-150–mediated Aflibercept Protein Expression

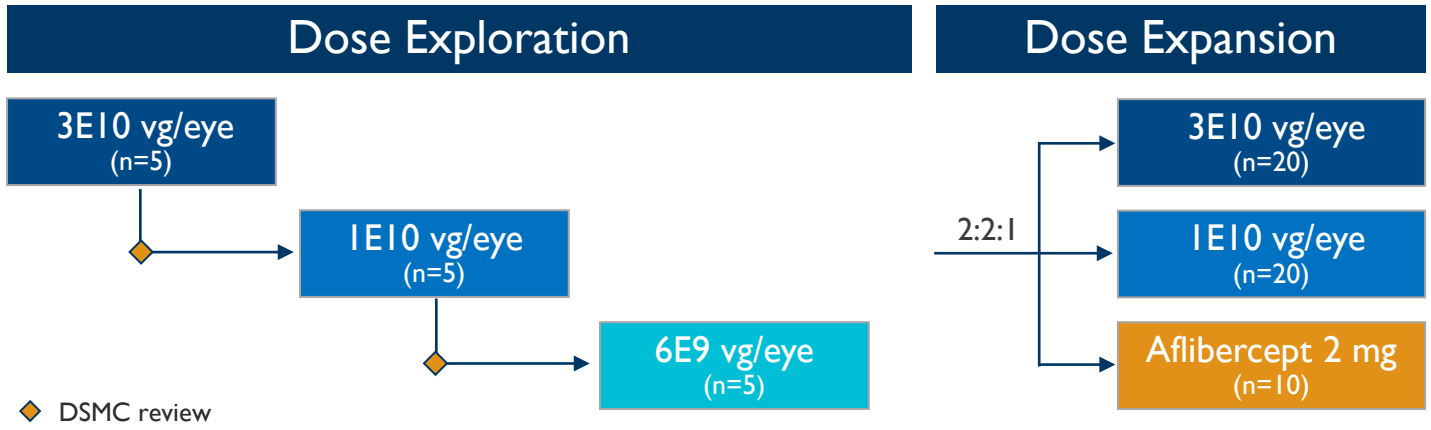


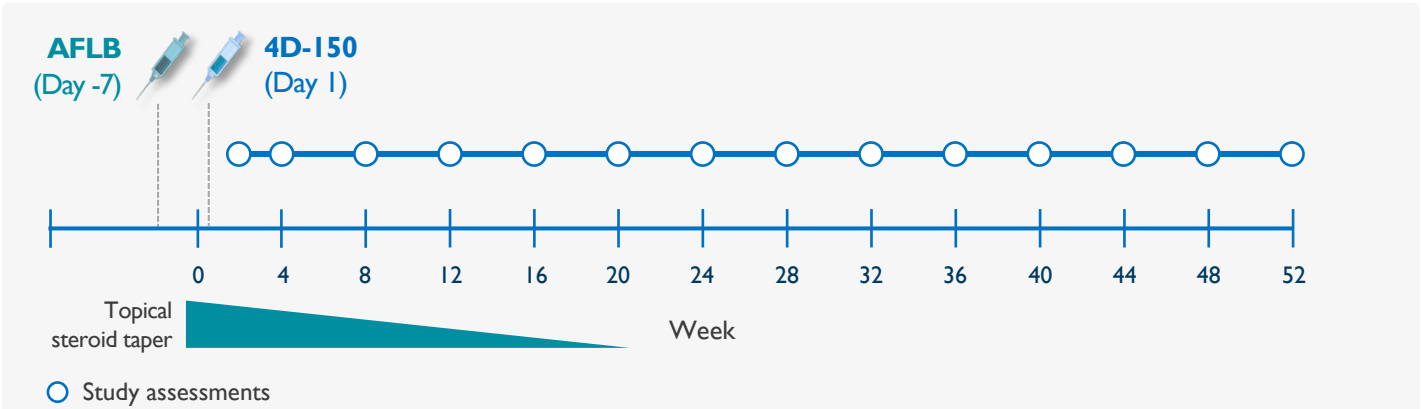
Mean ±SEM secreted free aflibercept protein expression 4 weeks after intravitreal administration of 4D-150 1×10^{12} vg/eye to NHPs. N=2 NHPs; 4 eyes. NHP, nonhuman primates.

4D-150 Phase 1/2 Clinical Trial

OBJECTIVE: EVALUATE SAFETY, TOLERABILITY, AND CLINICAL ACTIVITY

Study Design





Key Inclusion Criteria*

- Age ≥50 years
- CNV secondary to AMD
- ≥25 (~20/320) and ≤78 (~20/32) ETDRS letters†
- Clinical response to anti-VEGF in prior 12 months
- ≥6 anti-VEGF injections within the last 12 months

Primary Endpoint

- Incidence and severity of TEAEs and SAEs

Key Secondary Endpoints

- % change, annualized anti-VEGF injection rate
- % of subjects requiring supplemental aflibercept
- Number of supplemental aflibercept injections
- BCVA change from baseline
- CST change from baseline

*Dose exploration phase. †Sentinel subject. AMD, Age-related macular degeneration; BCVA, best corrected visual acuity; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; TEAE, treatment emergent adverse event; SAE, serious adverse event; VEGF, vascular endothelial growth factor.

Baseline Characteristics

ANALYSIS POPULATION: ALL ENROLLED PARTICIPANTS (N=15)

Characteristic	$3x10^{10}$ vg/eye (N=5)	$1x10^{10}$ vg/eye (N=5)	$6x10^{9}$ vg/eye (N=5)	Total (N=15)
Mean ±SE age, years	79 ±3.9	79 ±4.1	76 ±4.9	78 ±4.0
Female, n (%)	5 (100)	3 (60)	3 (60)	11 (73)
Race, n (%)				
White	5 (100)	5 (100)	4 (80)	14 (93)
Asian	0	0	1 (20)	1 (7)
Mean ±SE BCVA, ETDRS letters	55 ±7.4	65 ±3.4	75 ±4.0	65 ±3.6
Snellen equivalent	20/80	20/50	20/32	20/50
Mean ±SE central subfield thickness, μm	424 ±27.0	351 ±44.4	402 ±85.0	392 ±31.8
Mean ±SE time since diagnosis	3.5 ±0.8	2.6 ±0.5	4.7 ±1.4	3.6 ±1.0
Mean prior annualized injection rate*	10.8	8.3	8.7	9.3

- As of 3 April 2023, all participants have completed ≥6 months of follow-up (range, 6–16 months)

Data cutoff date, 3 April 2023. *Includes Day -7 AFLB injection. BCVA, best corrected visual acuity; VEGF, vascular endothelial growth factor.

Overall Safety Summary

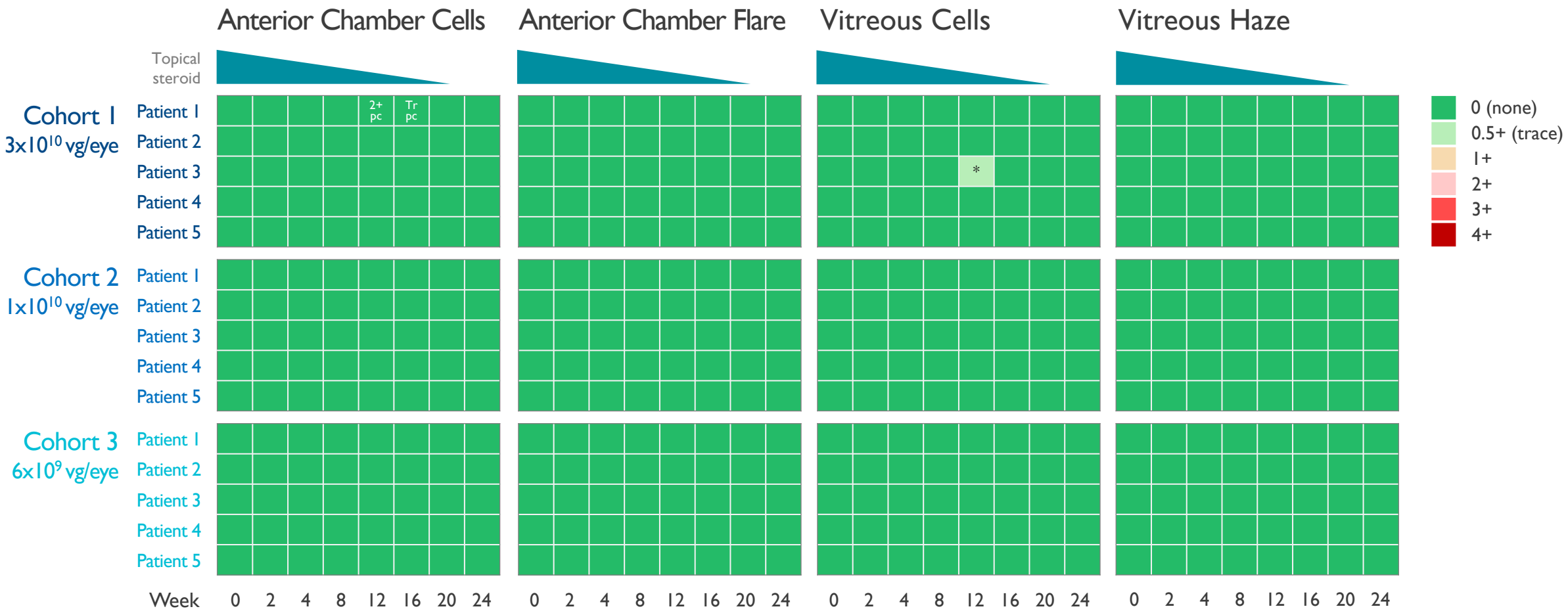
24 WEEKS OF FOLLOW-UP: 4D-150 SAFE AND WELL TOLERATED

- No dose-limiting toxicities
- No 4D-150–related SAEs
- 4D-150–related TEAEs (n=2)
  - $3x10^{10}$ vg/eye group: pigmented anterior chamber cells (mild, n=1), mixed vitreous cells (mild, n=1)
- No eyes with SUN or NEI Grade ≥1+ WBC, flare, or haze
- No hypotony, no intraocular inflammation requiring intervention, no endophthalmitis, no retinal vasculitis, no choroidal effusions, no retinal artery occlusion

Data cutoff date, 3 April 2023. NEI, National Eye Institute; SAE, serious adverse event; SUN, Standardization of Uveitis Nomenclature; TEAE, treatment emergent adverse events, WBC, white blood cells.

Ophthalmic Examination

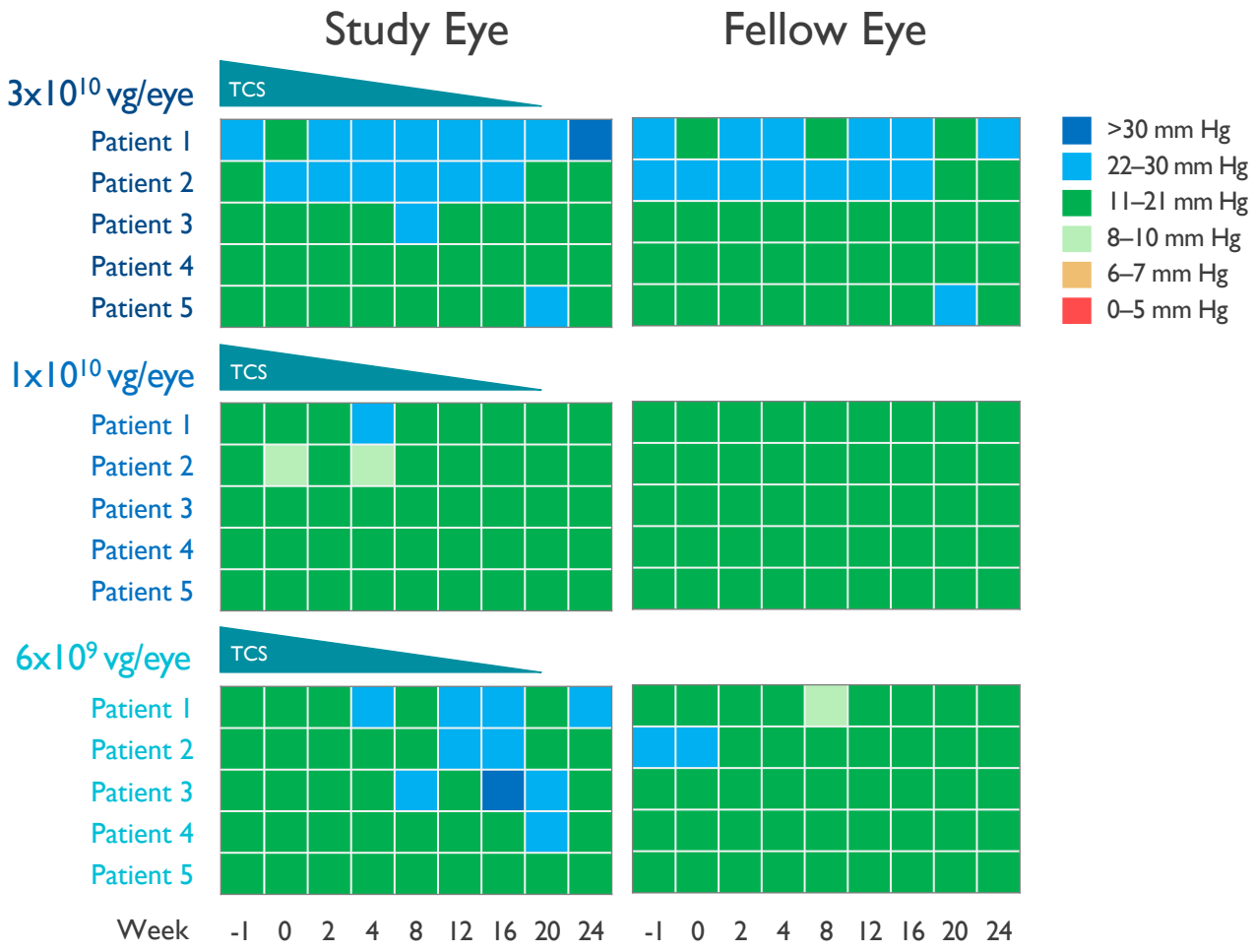
NO SUN OR NEI GRADE ≥1+ WBC, FLARE, OR HAZE

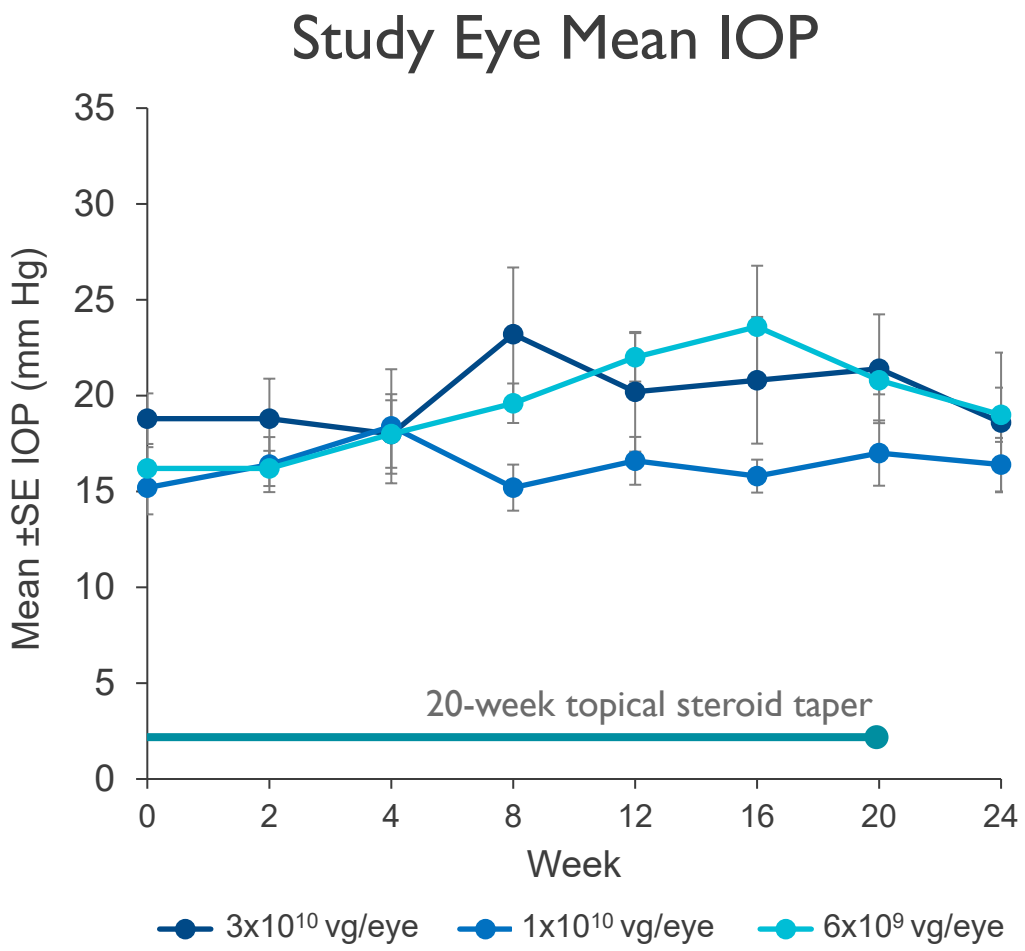


- 14/15 participants did not require steroids after completion of the protocol-mandated 20-week prophylactic topical steroid taper

Data cutoff date, 3 April 2023. *Trace mixed pigmented and unpigmented cells. NEI, National Eye Institute; PC, pigmented cells; SUN, Standardization of Uveitis Nomenclature; Tr, trace.

Intraocular Pressure (IOP)

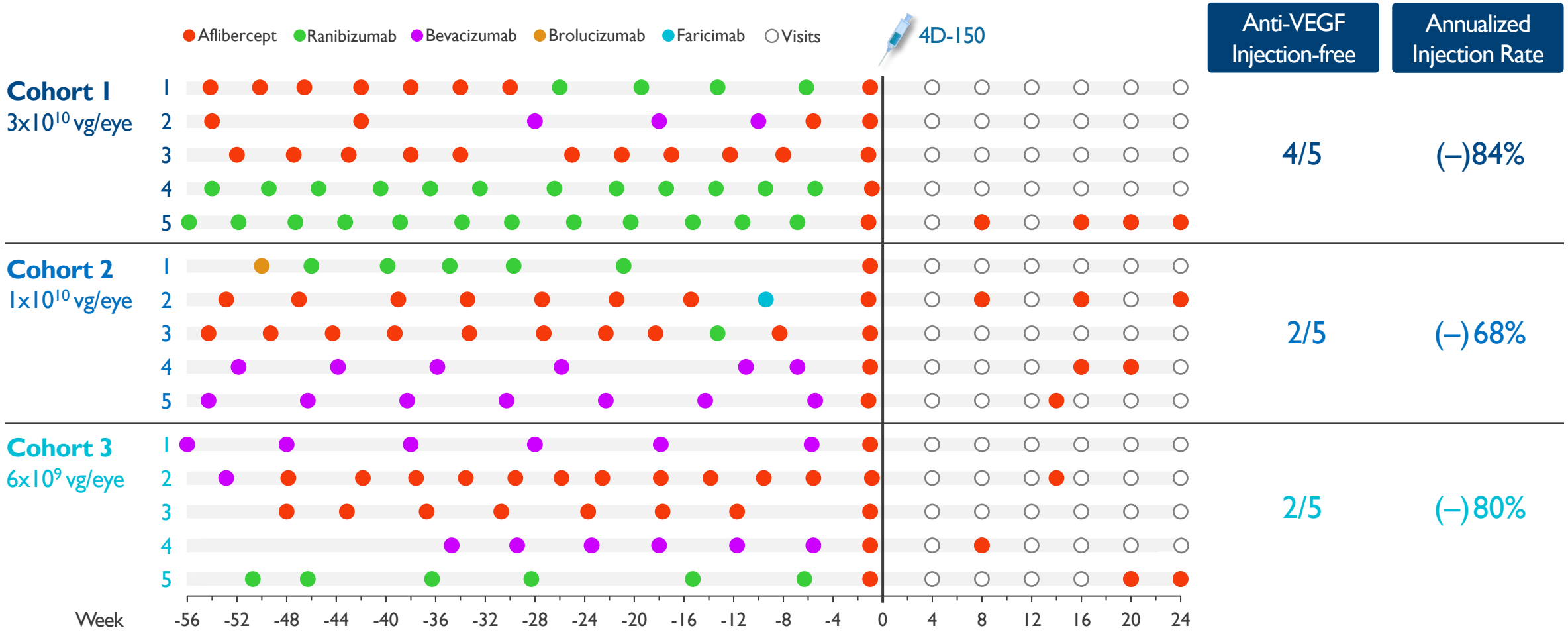




Data cutoff date, 3 April 2023. SE, standard error; TCS, topical corticosteroid.

Anti-VEGF Injections at Week 24

UP TO 84% REDUCTION IN ANNUALIZED ANTI-VEGF INJECTION RATE



	Anti-VEGF Injection-free	Annualized Injection Rate
Cohort 1	4/5	(–)84%
Cohort 2	2/5	(–)68%
Cohort 3	2/5	(–)80%

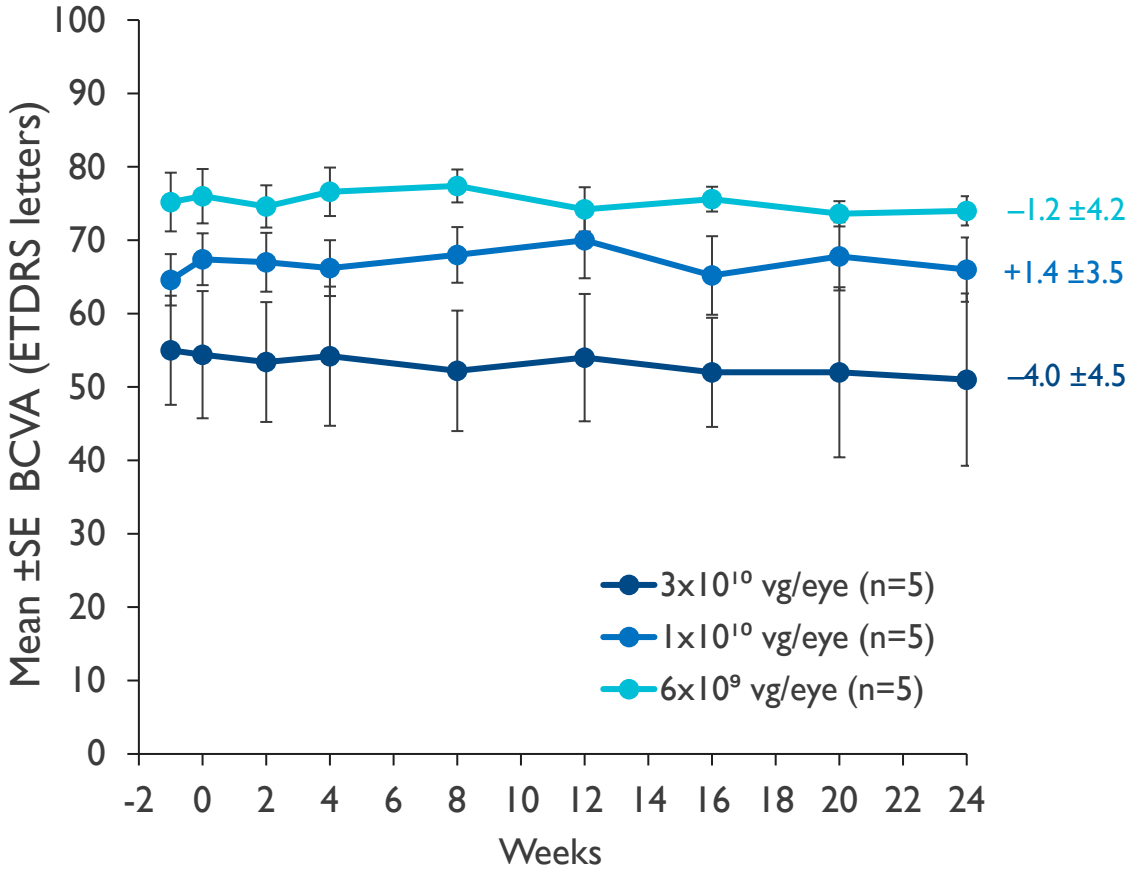
Anti-VEGF Injection Criteria: Loss of ≥10 letters from baseline in BCVA attributable to intraretinal or subretinal fluid; increase in CST >75 µm from baseline, confirmed by central reading center; presence of new vision-threatening hemorrhage due to wet AMD as determined by investigator.

Data cutoff date, 3 April 2023.

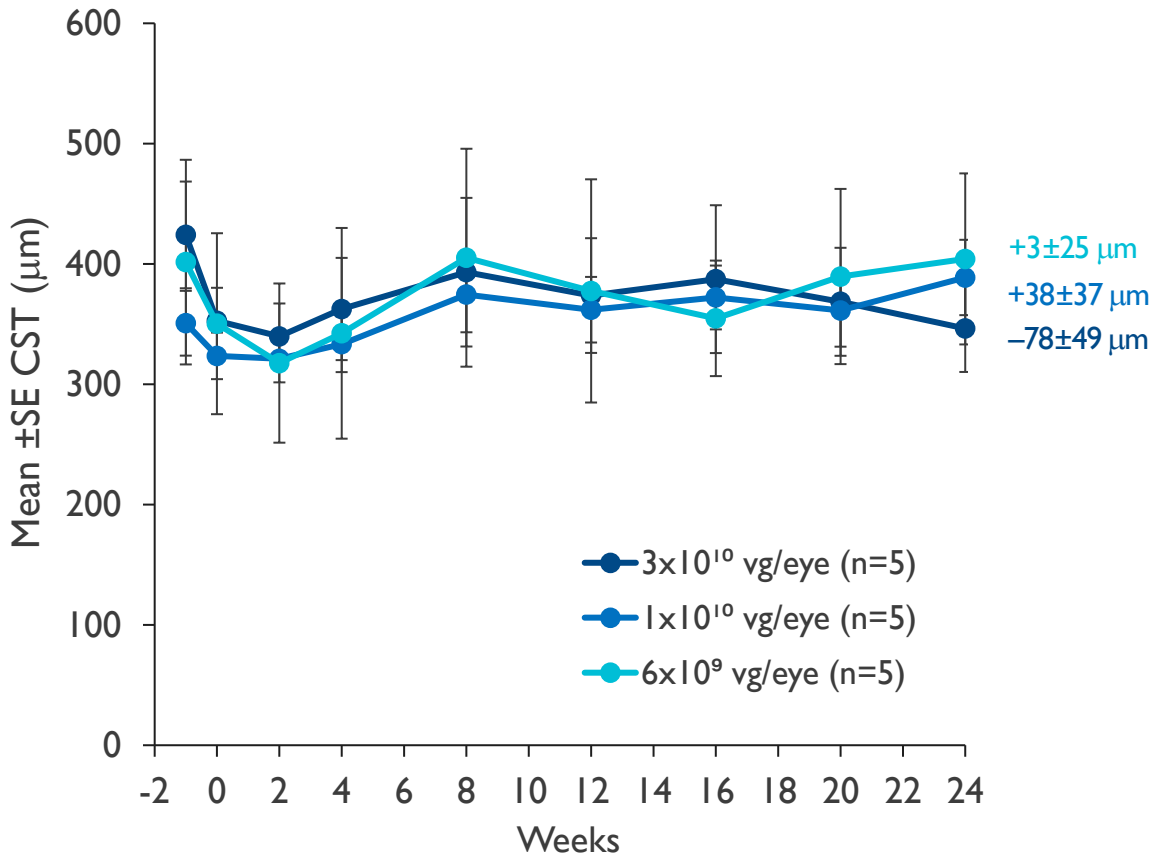
Visual and Anatomic Outcomes

STABLE VISUAL ACUITY AND CENTRAL SUBFIELD THICKNESS THROUGH WEEK 24

Best Corrected Visual Acuity

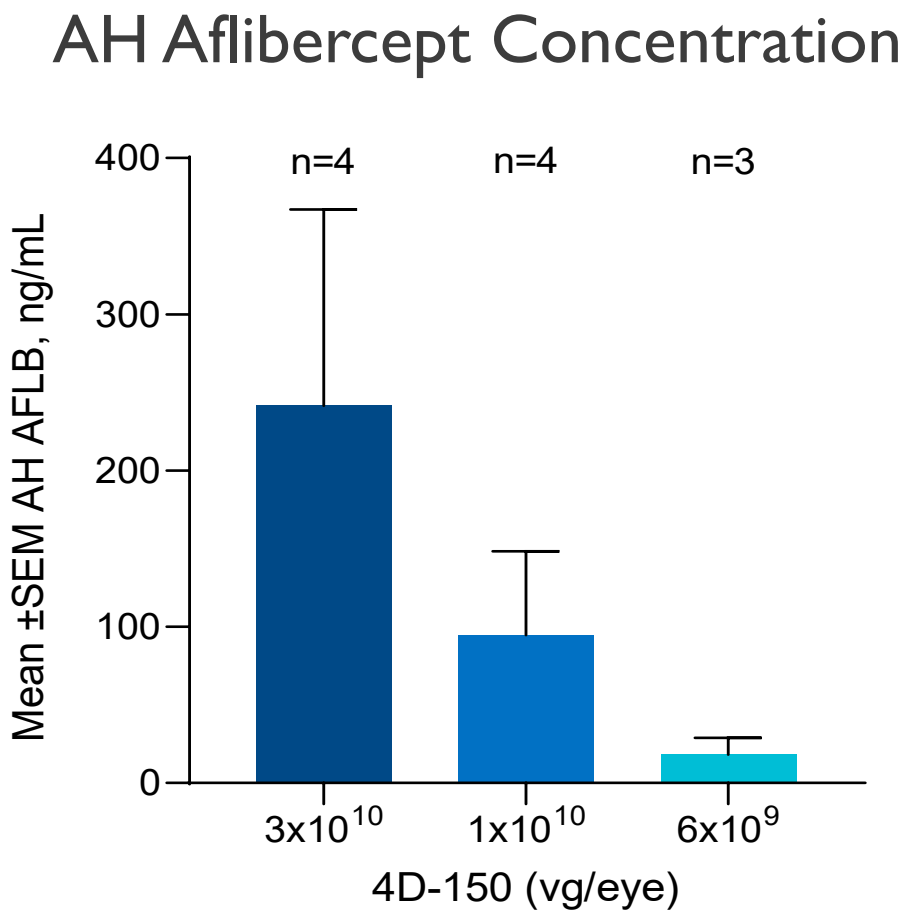


Central Subfield Thickness



Data cutoff date, 3 April 2023. BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; SE, standard error.

Aqueous Humor Aflibercept Concentrations (Week 12)



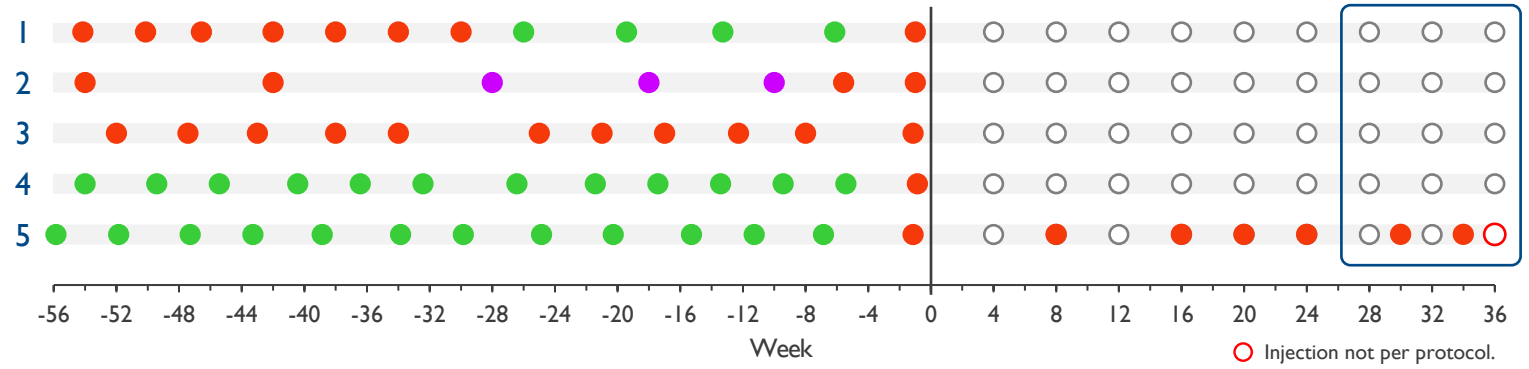
- Detectable aflibercept in AH is consistent with predicted therapeutic concentrations of 4D-150 in the retina
- Dose-related aflibercept concentrations observed in aqueous humor
  - 12 of 15 participants reached Week 12 without receiving supplemental aflibercept injection
  - 11 of 12 samples available at the time of analysis
  - Aflibercept transgene expression detected at Week 12 in 10 of 11 (91%) samples

Data cutoff date, 3 April 2023. *Analysis pending (n=1). AFLB, aflibercept; AH, aqueous humor; SEM, standard error of measurement.

Clinical Assessments Through Week 36

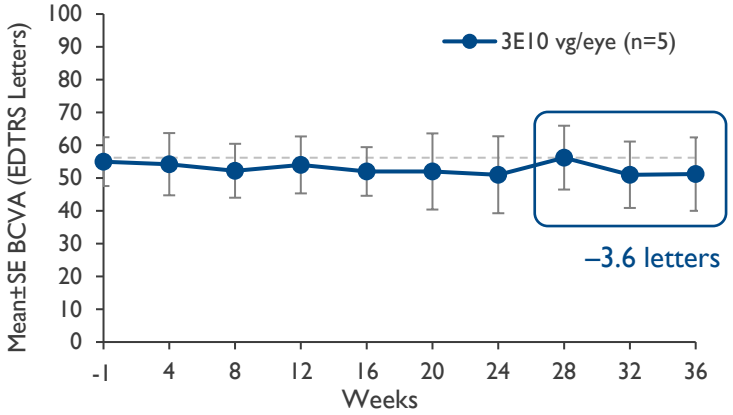
$3x10^{10}$ vg/eye DOSE COHORT

Anti-VEGF Injections

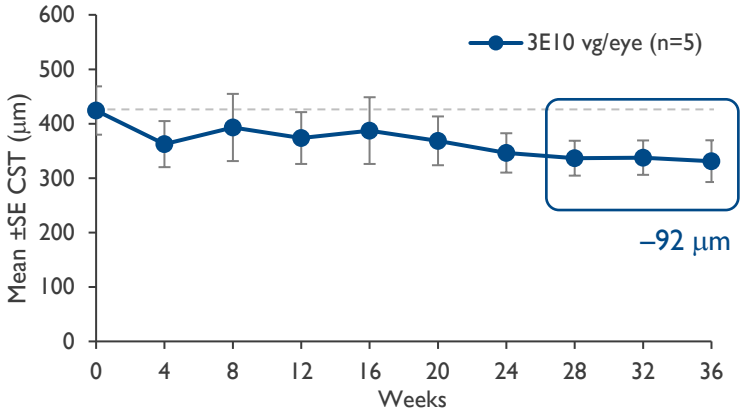


- 4/5 (80%) participants anti-VEGF injection-free

Best Corrected Visual Acuity



Central Subfield Thickness



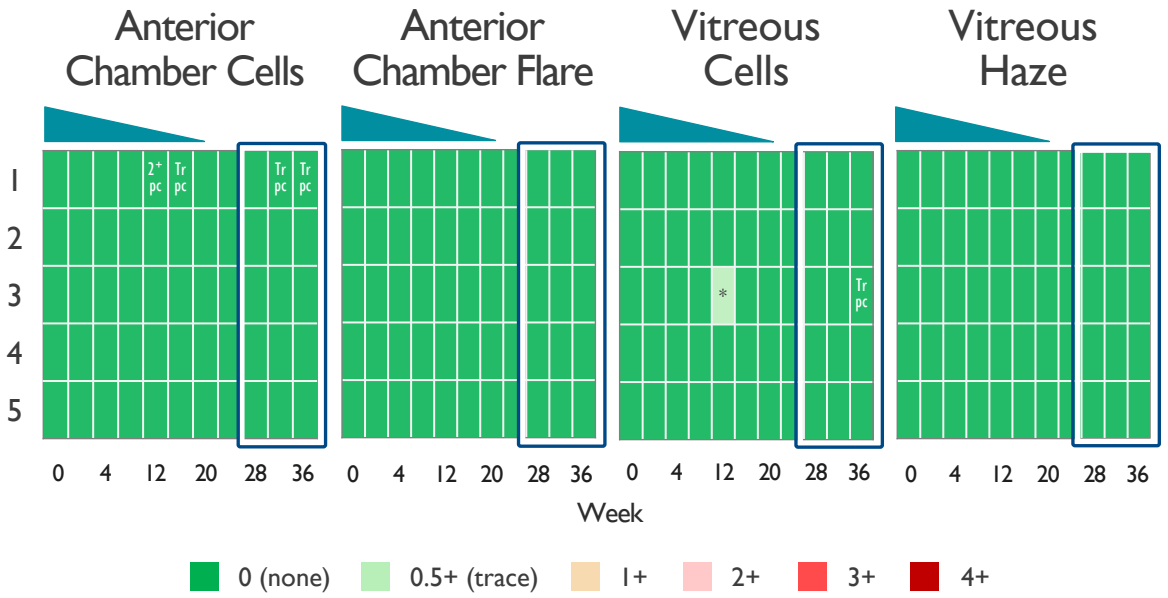
- Stable BCVA and improved CST through Week 36

Data cutoff date, 3 April 2023. BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; SE, standard error.

Safety Assessments Through Week 36

$3x10^{10}$ vg/eye DOSE COHORT

Ophthalmic Exam



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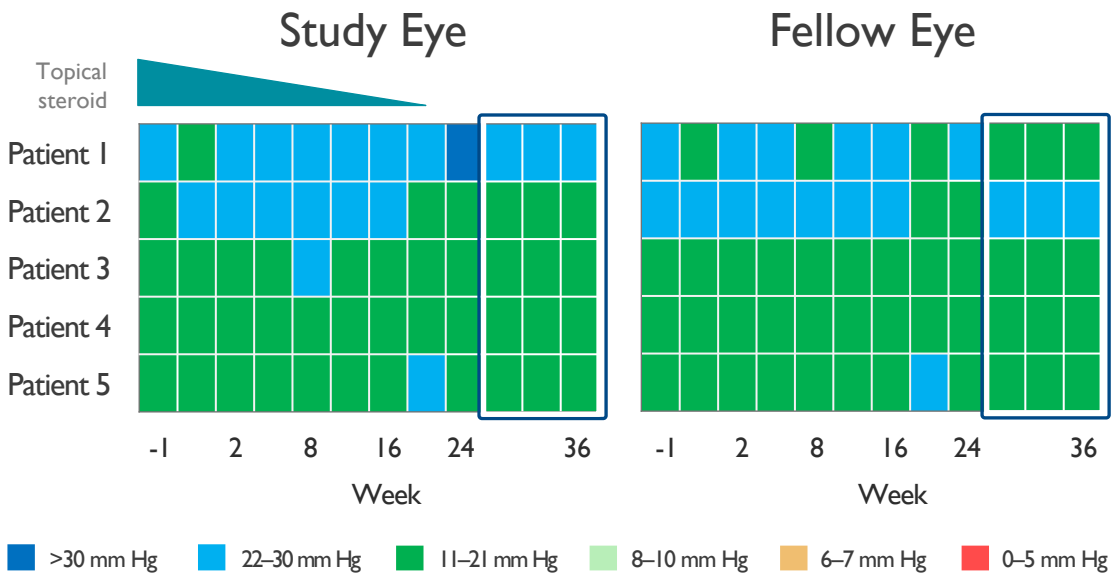
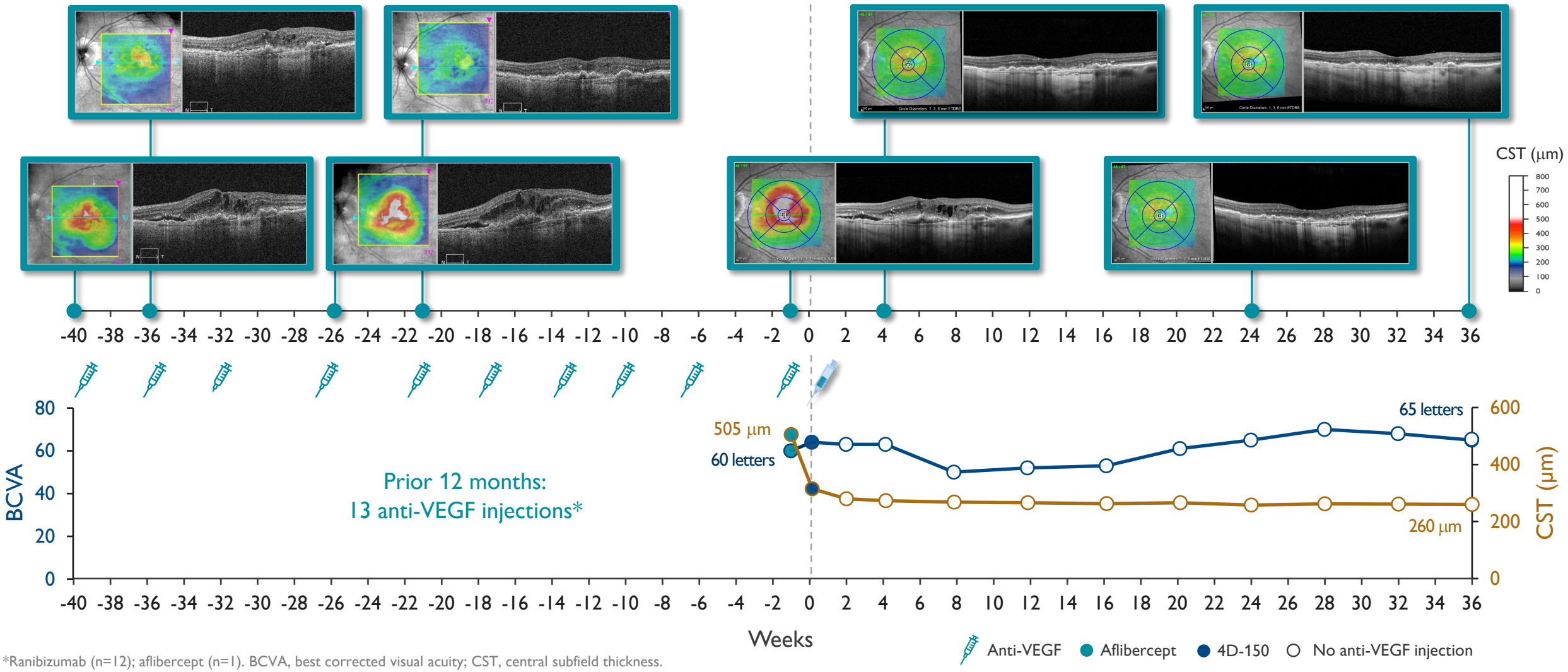


- No eyes with SUN or NEI Grade ≥1+ WBC, flare, or haze
- No hypotony, no intraocular inflammation requiring intervention, no endophthalmitis, no retinal vasculitis, no choroidal effusions, no retinal artery occlusion

Data cutoff date, 3 April 2023. *Trace mixed pigmented and unpigmented cells. NEI, National Eye Institute; PC, pigmented cells; SUN, Standardization of Uveitis Nomenclature; WBC, white blood cells; Tr, trace.

Case Study

89-YEAR-OLD FEMALE (3x10[10] vg/eye)



*Ranibizumab (n=12); aflibercept (n=1). BCVA, best corrected visual acuity; CST, central subfield thickness.

Conclusions

- Intravitreal administration of 4D-150 in patients with wet AMD was safe and generally well tolerated at doses ranging from $6x10^9$ to $3x10^{10}$ vg/eye through Week 24
  - No dose-limiting toxicities and no 4D-150–related serious adverse events
  - 14/15 participants with no intraocular inflammation
  - No hypotony
- Clinical activity demonstrated across all 4D-150 dose cohorts through Week 24
  - Up to 84% reduction in mean annualized anti-VEGF injection rate through Week 24, stable BCVA and CST
- $3x10^{10}$ vg/eye dose resulted in 4/5 patients (with high anti-VEGF need) injection-free at Week 36 with stable BCVA and improved CST
- Currently enrolling randomized Phase 2 dose expansion study (enrollment >50% complete)
  - 4D-150 ($1x10^{10}$ vg/eye or $3x10^{10}$ vg/eye) vs aflibercept 2 mg

Acknowledgments