A Phase 1/2 Clinical Trial Evaluating 4D-150, a Dual-transgene Intravitreal Gene Therapy in Patients with Wet Age-Related Macular Degeneration: Interim 9-Month Results

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Disclosures

Atsena Therapeutics
- Consultant
- Stock options

AGTC/Syncona
- Investigator

Foundation Fighting Blindness
- Investigator

Alkeus
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Janssen
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Belite Bio
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Gyroscope
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Kiora Pharmaceuticals
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- Stock options

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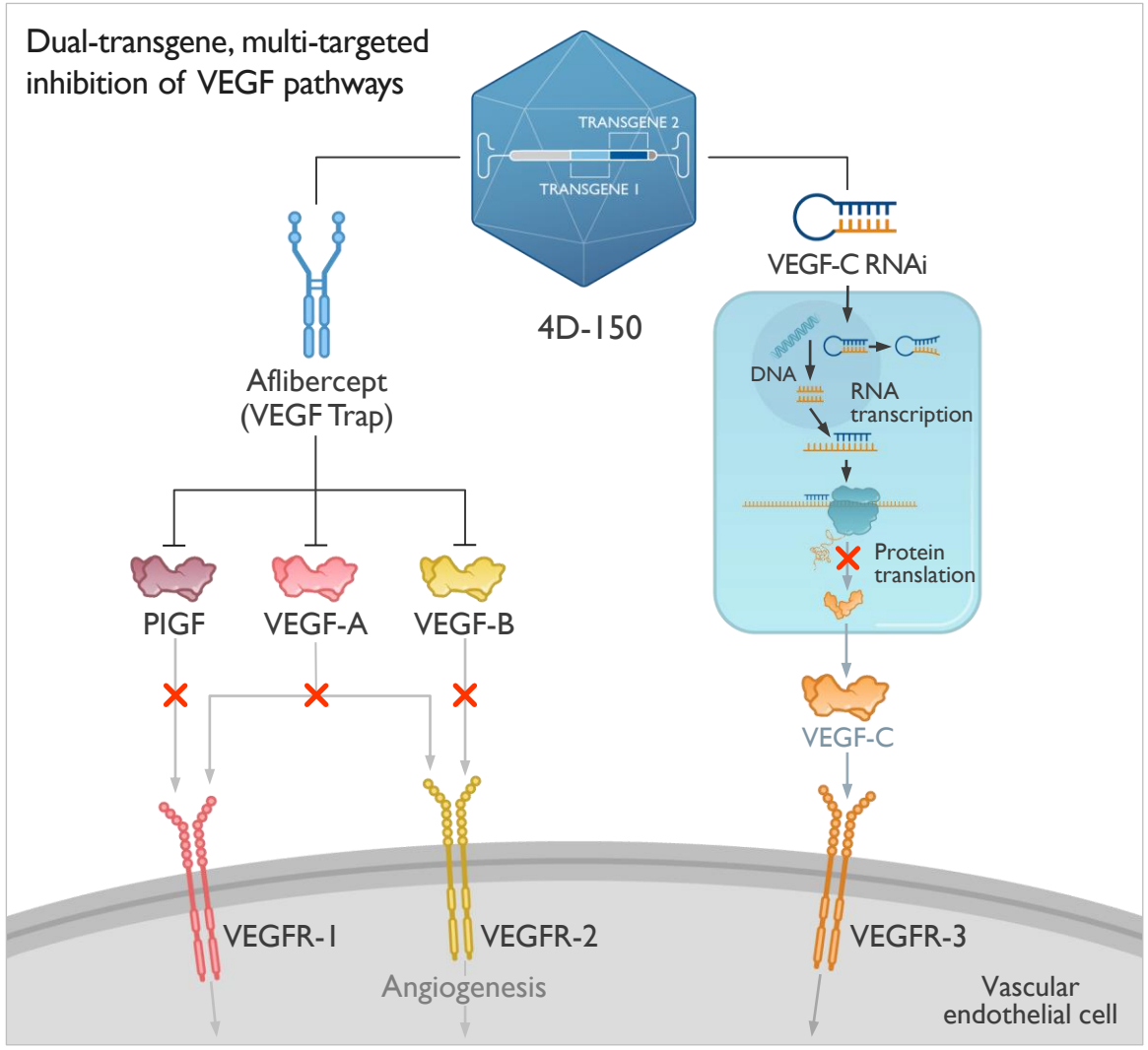
4D-150: Overview

- 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)

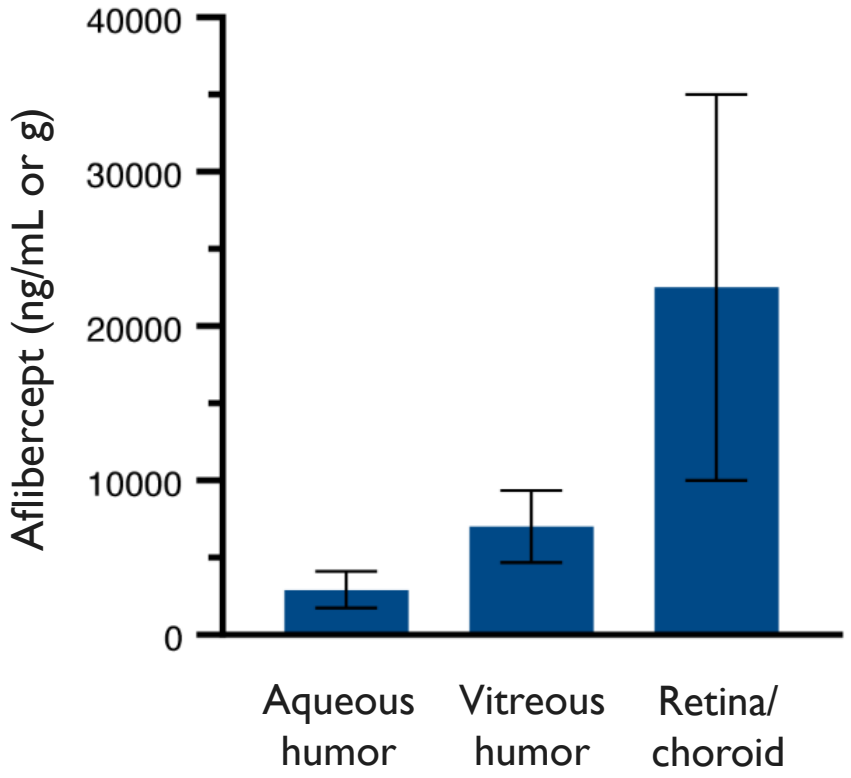


PlGF, placental growth factor; VEGF, vascular endothelial growth factor.

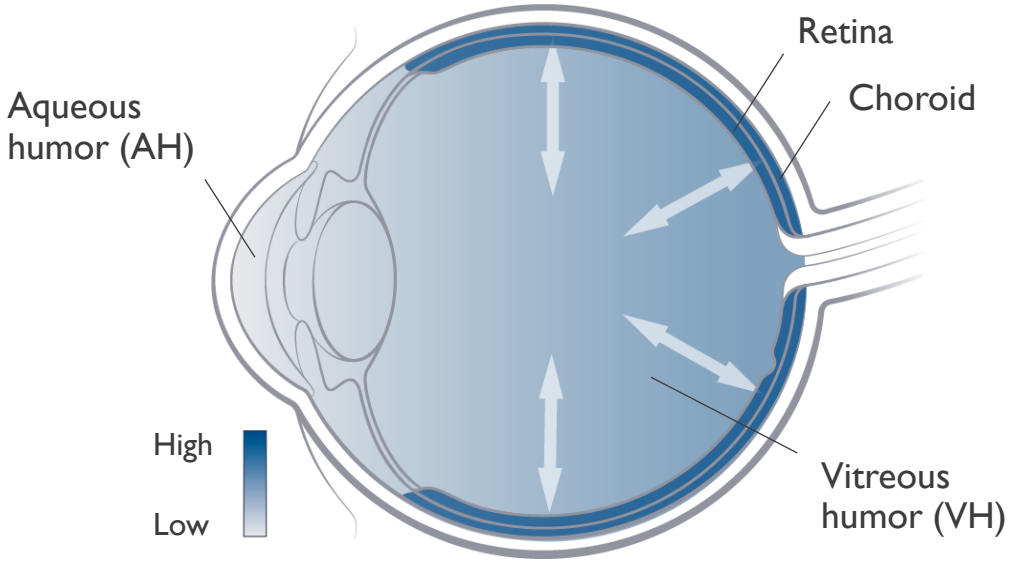
Intravitreal 4D-150 Biodistribution: Therapeutic Levels of Aflibercept

RETINOTROPIC R100 VECTOR FACILITATES HIGH-LEVEL EXPRESSION WITHIN THE RETINA

Aflibercept Concentration (NHP)*



4D-150–mediated Aflibercept Protein Expression

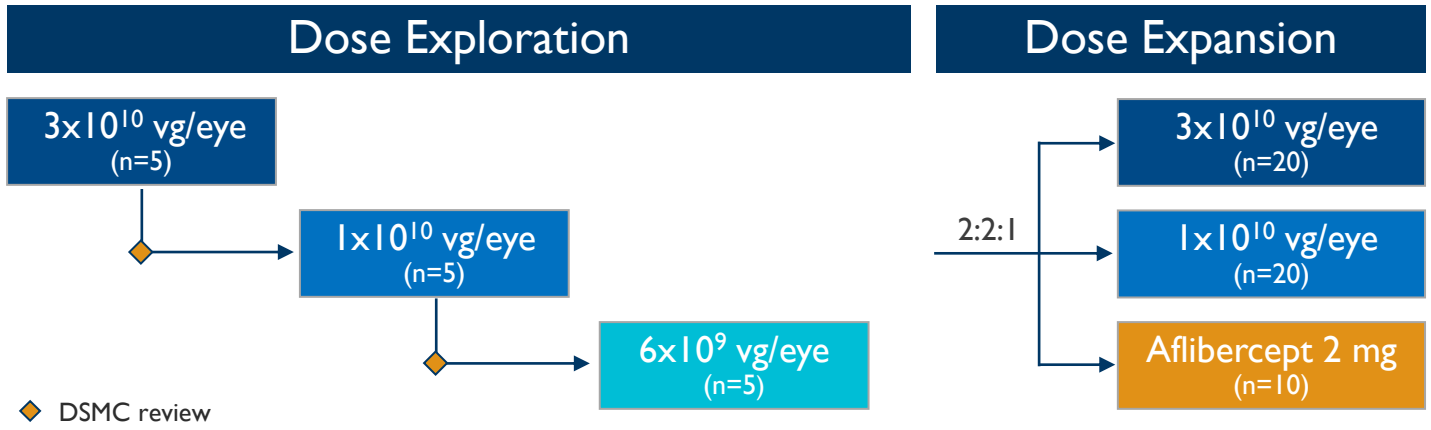


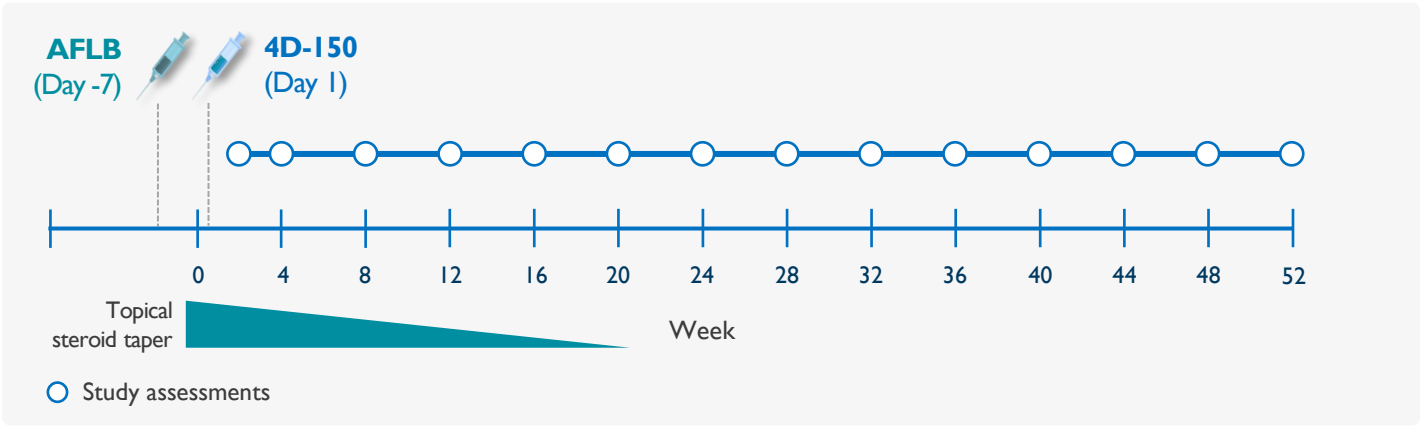
*Mean ±SEM secreted free aflibercept protein expression 4 weeks after intravitreal administration of 4D-150 1×10^{12} vg/eye to NHPs. N=2 NHPs; 4 eyes. NHP, nonhuman primates.

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)

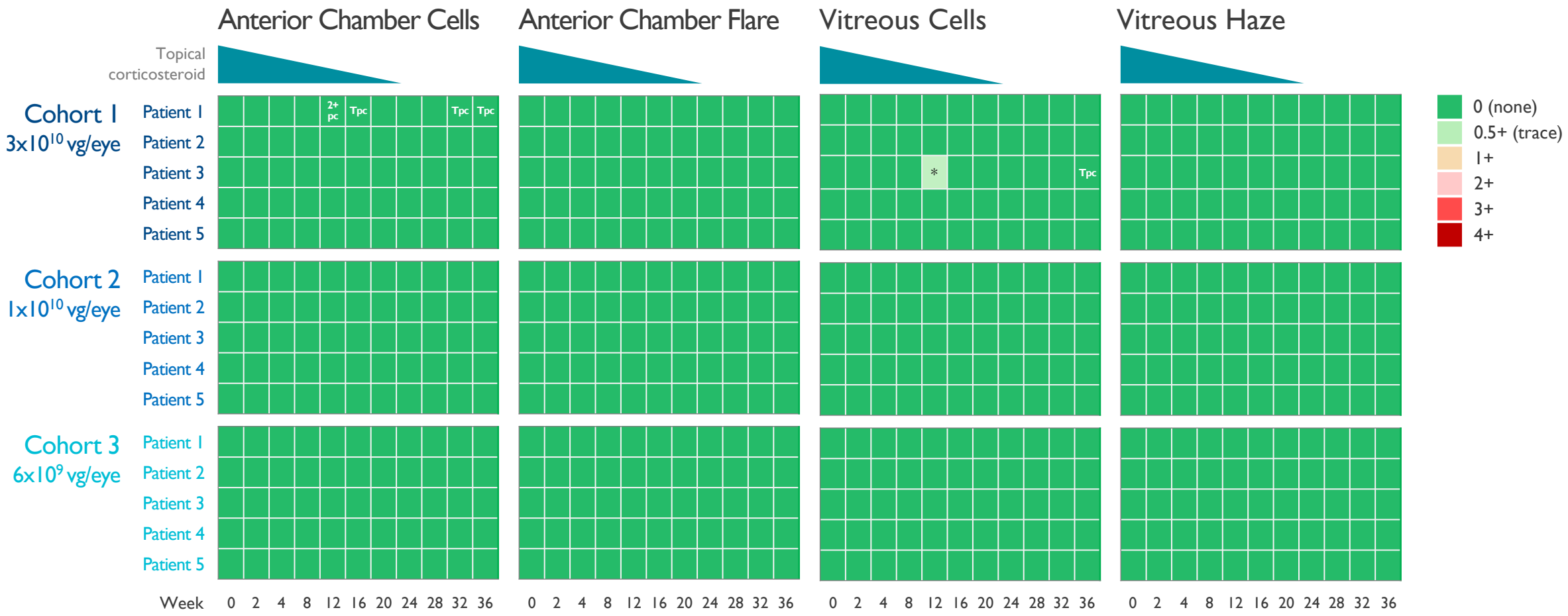
Characteristic	$3x10^{10}$ vg/eye (N=5)	$1x10^{10}$ vg/eye (N=5)	$6x10^{9}$ vg/eye (N=5)	Total (N=15)
Mean ±SE age, years	79 ±3.9	79 ±4.1	76 ±4.9	78 ±4.0
Female, n (%)	5 (100)	3 (60)	3 (60)	11 (73)
Race, n (%)				
White	5 (100)	5 (100)	4 (80)	14 (93)
Asian	0	0	1 (20)	1 (7)
Mean ±SE BCVA, ETDRS letters	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 July 2023, all participants have completed ≥9 months of follow-up

Data cutoff date, 3 July 2023. *Includes Day -7 AFLB injection. BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SE, standard error; VEGF, vascular endothelial growth factor.

Ophthalmic Examination

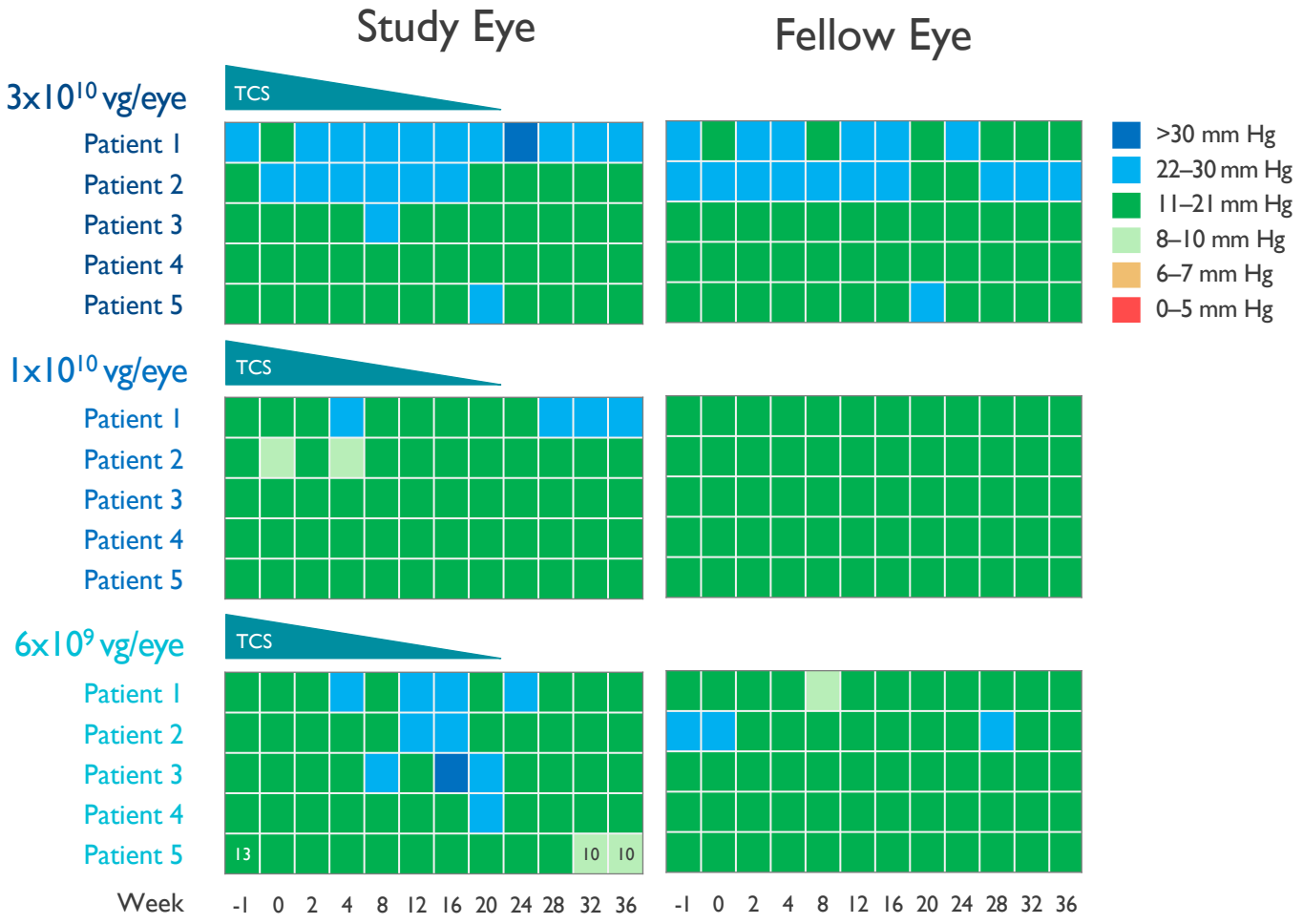
NO SUN OR NEI GRADE ≥1+ WBC, FLARE, OR HAZE

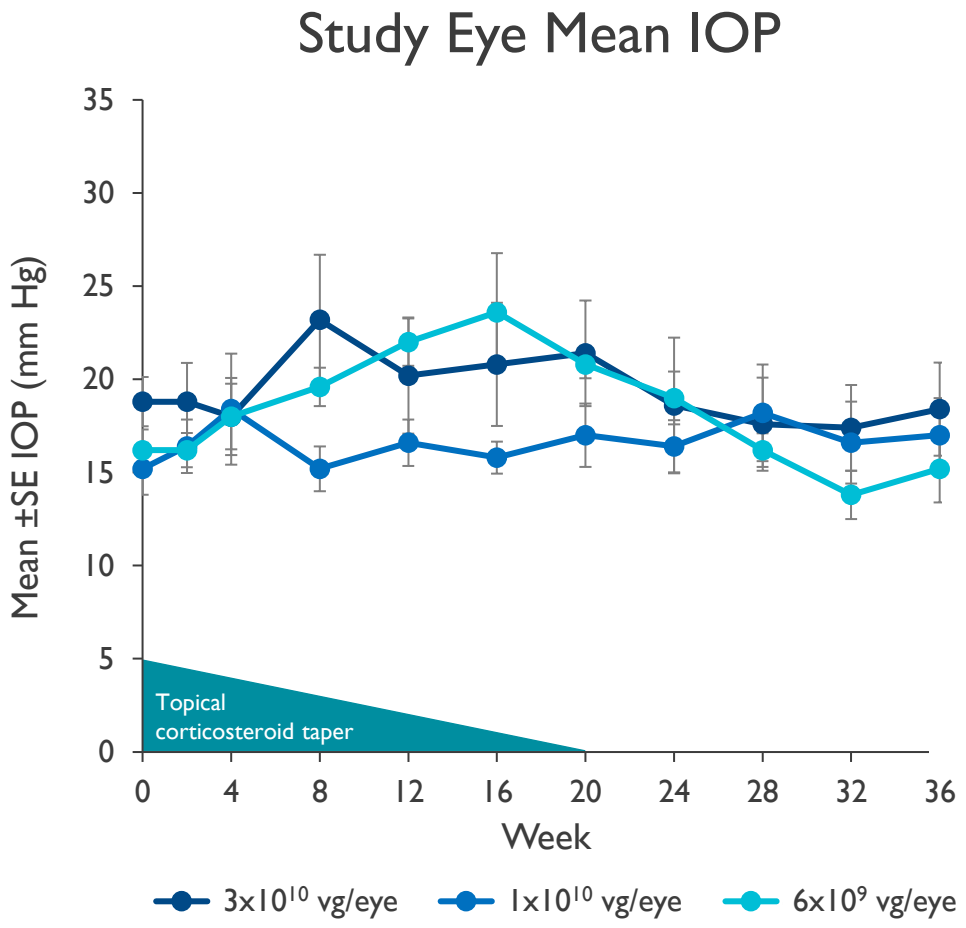


- 14/15 participants did not require steroids after completion of the protocol-mandated 20-week prophylactic topical steroid taper

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

Intraocular Pressure (IOP)

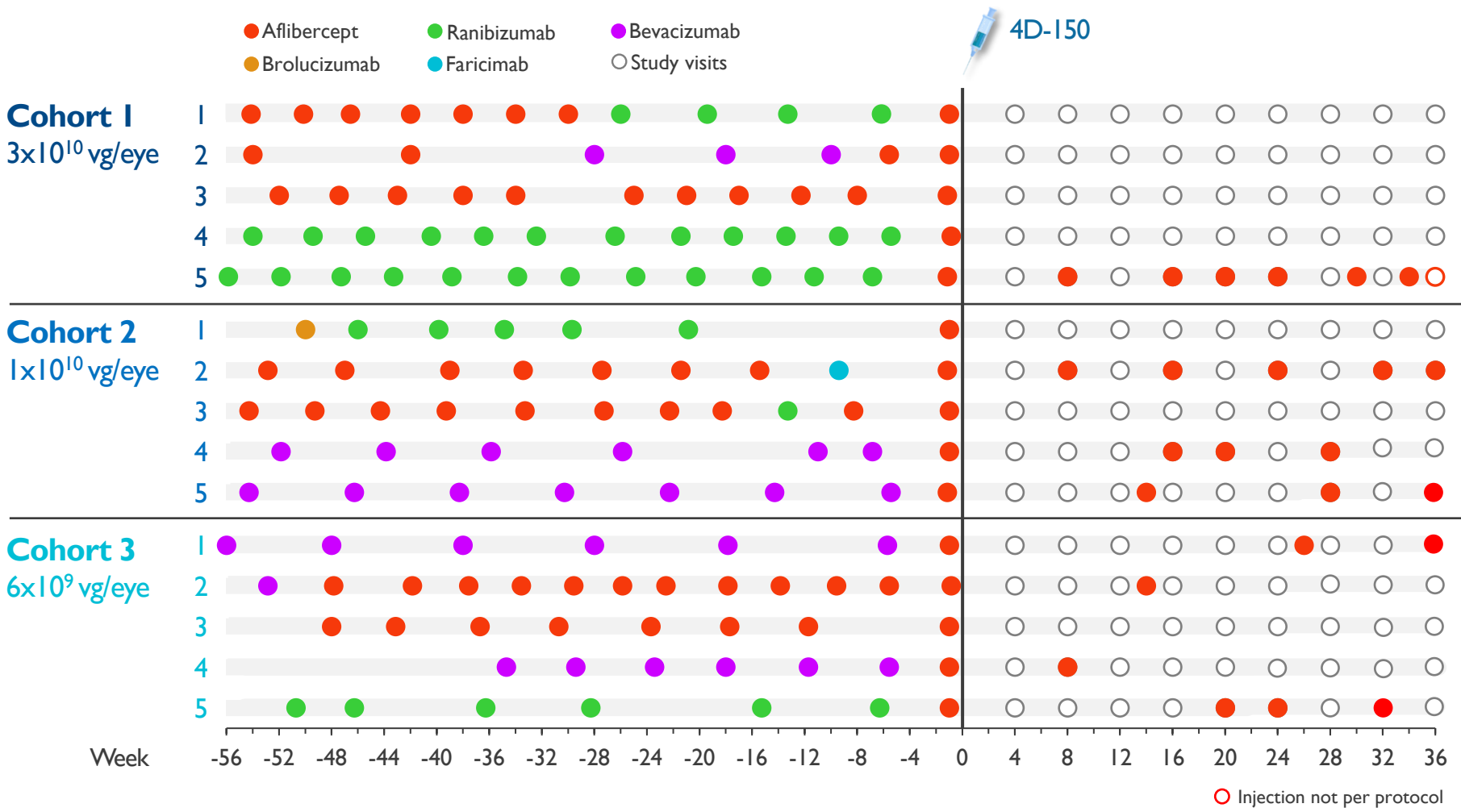




Data cutoff date, 3 July 2023. SE, standard error; TCS, topical corticosteroid.

Anti-VEGF Injections at Week 36

UP TO 81% REDUCTION IN ANNUALIZED ANTI-VEGF INJECTION RATE



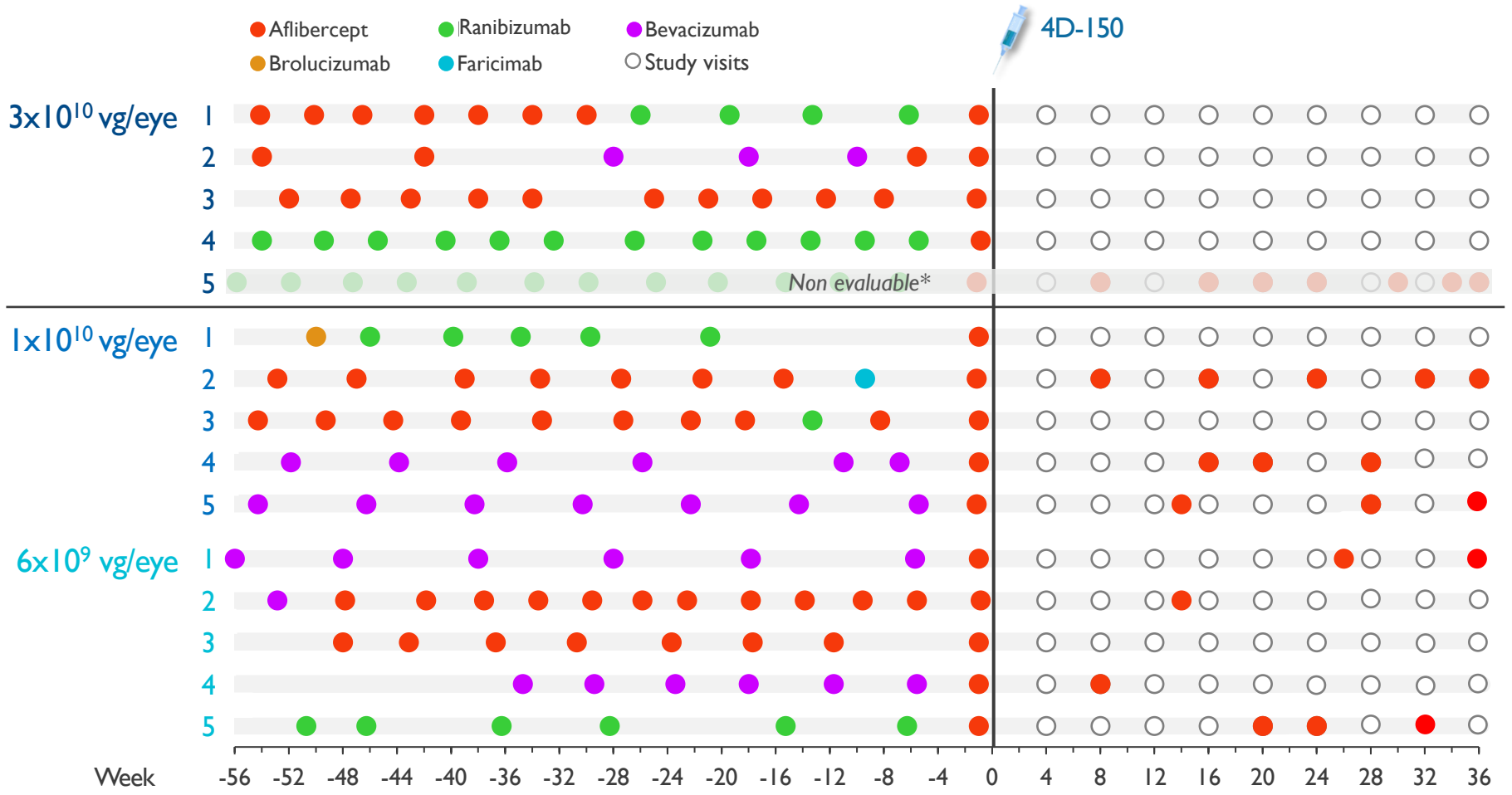
	Anti-VEGF Injection-free	Annualized Injection Rate
Cohort 1	4/5 (80%)	(–)81%
Cohort 2	2/5 (40%)	(–)64%
Cohort 3	1/5 (20%)	(–)77%

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 July 2023.

Anti-VEGF Injections at Week 36

4 OF 4 (100%) EVALUABLE PARTICIPANTS INJECTION-FREE AT HIGHEST DOSE ($3x10^{10}$ vg/EYE)



Durable injection-free: 4/4 (100%)

Injection-free: 3/10 (30%)

≤1 injection 5/10 (50%)

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.

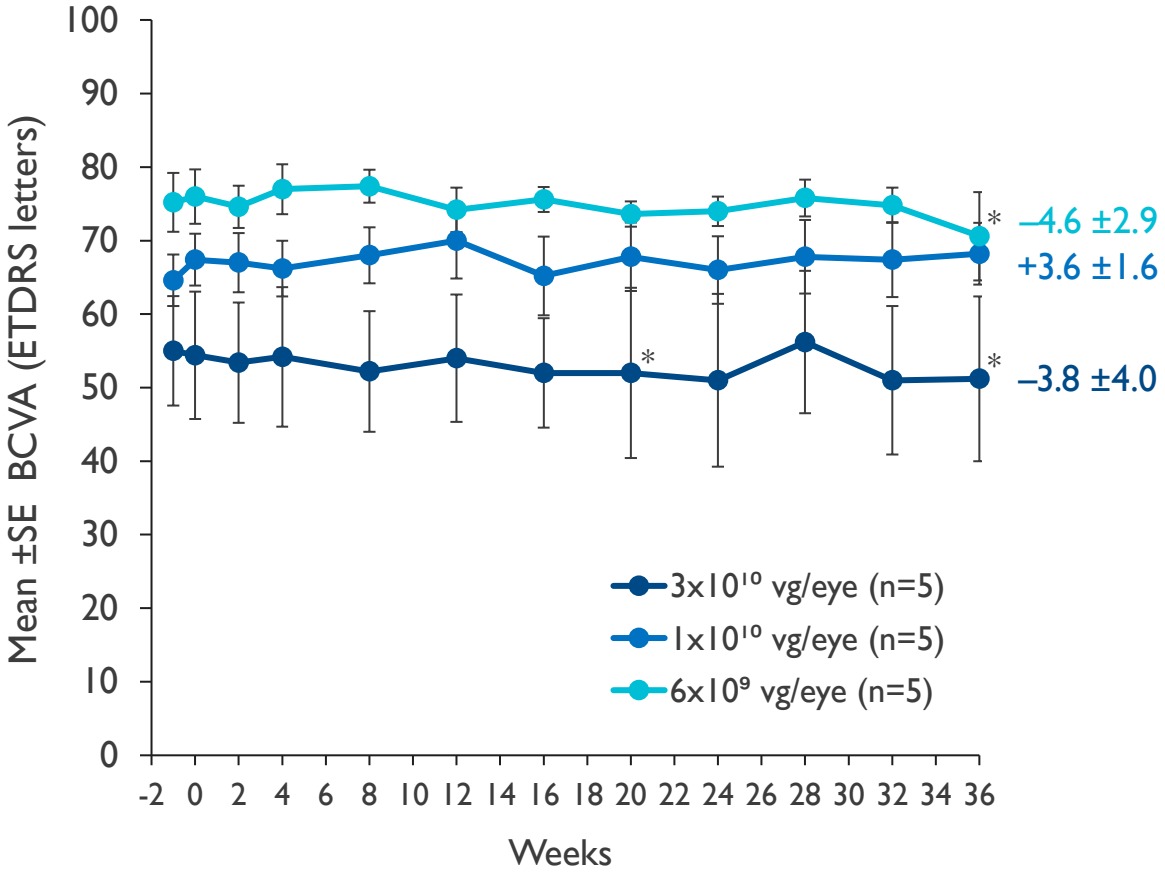
Data cutoff date, 3 July 2023.

*Progressive nuclear sclerotic cataract (Day -1), posterior subcapsular cataract (Week 16).

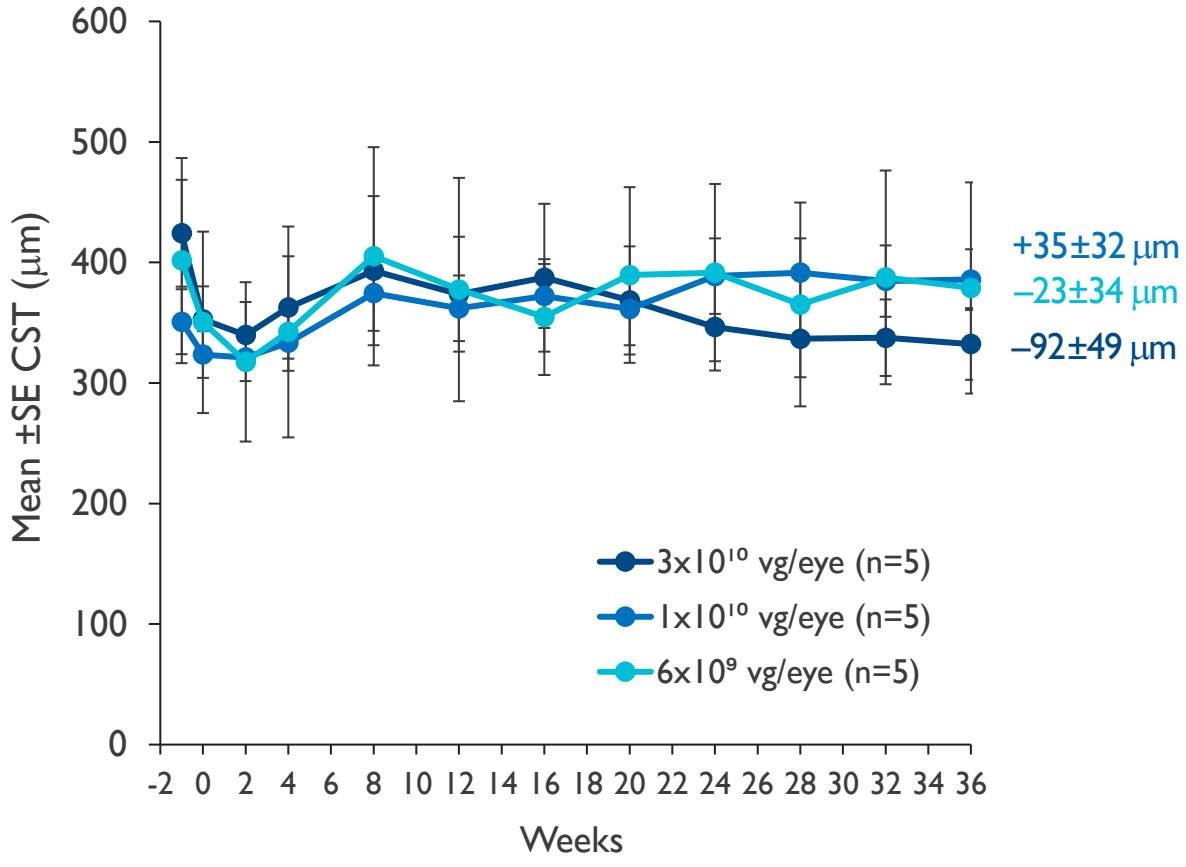
Visual and Anatomic Outcomes

STABLE VISUAL ACUITY AND CENTRAL SUBFIELD THICKNESS THROUGH WEEK 36

Best Corrected Visual Acuity

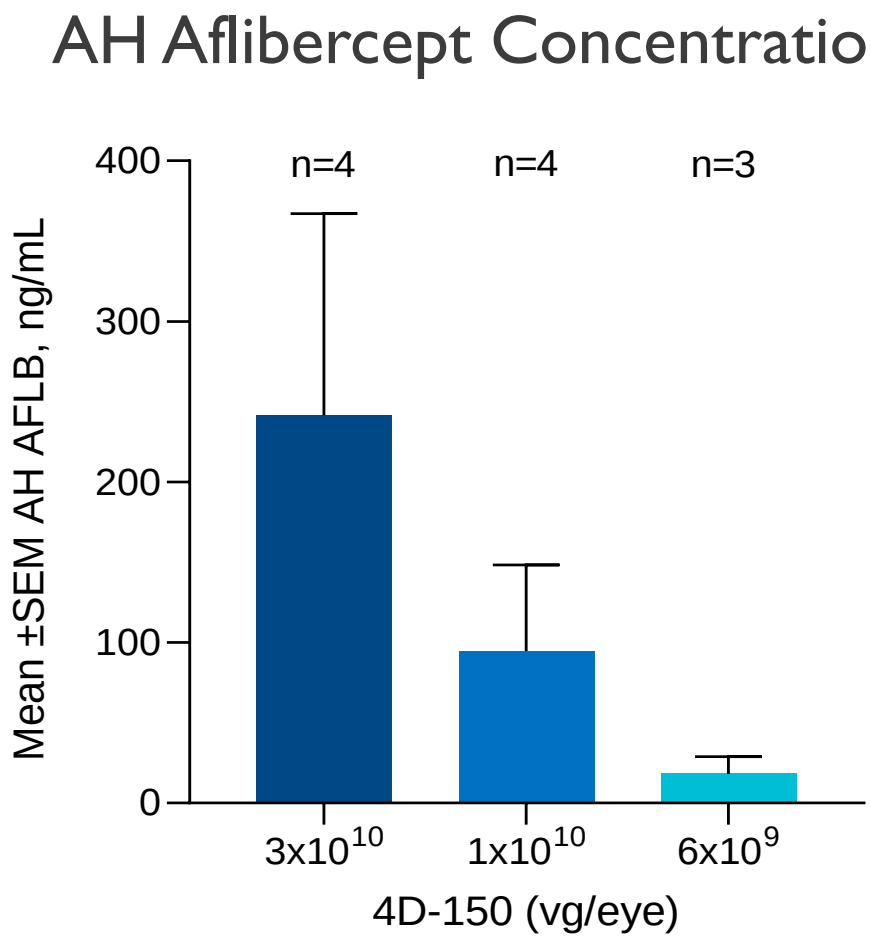


Central Subfield Thickness



Data cutoff date, 3 July 2023.* Includes one participant with newly diagnosed cataract. BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; SE, standard error.

Aqueous Humor Aflibercept Concentrations (Week 12)

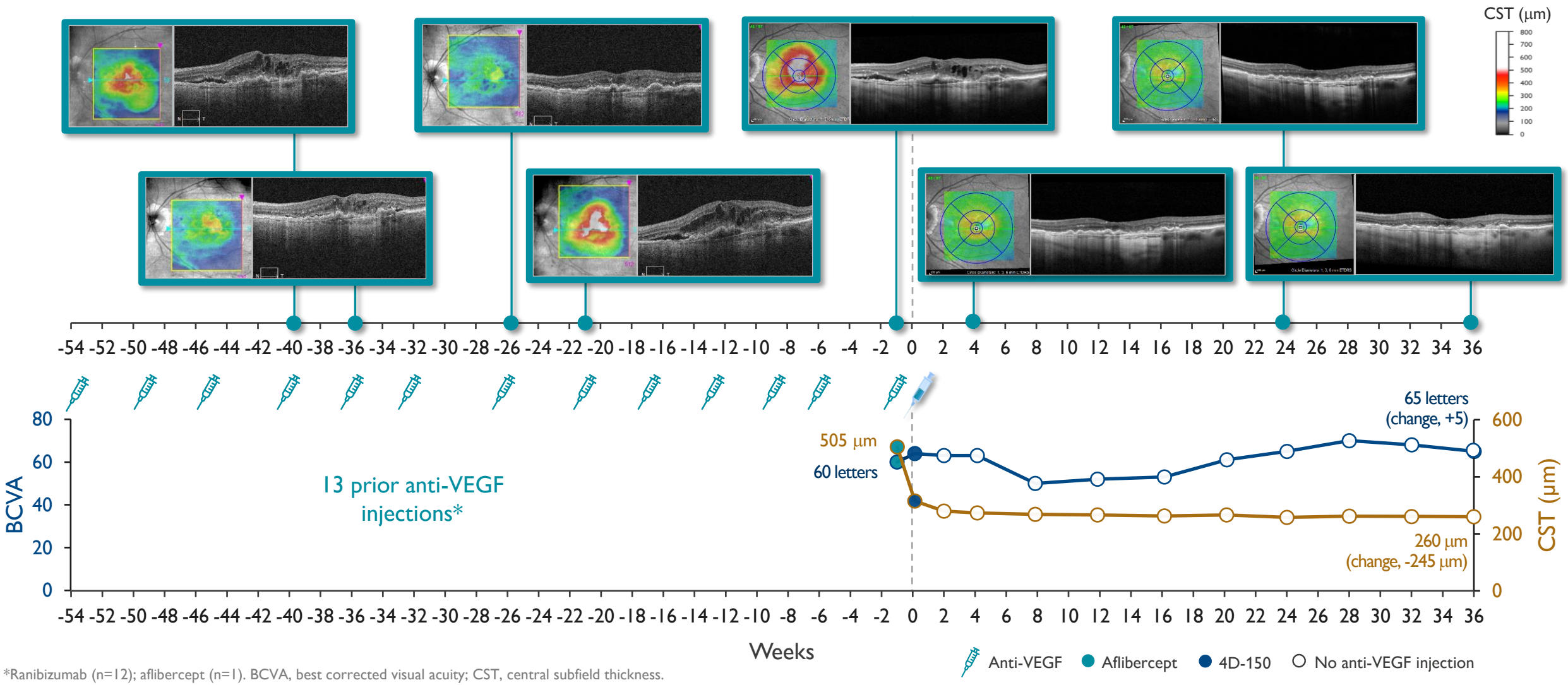


- Detectable aflibercept in AH is consistent with predicted therapeutic concentrations of 4D-150 in the retina
- Dose-related aflibercept concentrations observed in aqueous humor
  - 12 of 15 participants reached Week 12 without receiving supplemental aflibercept injection
  - 11 of 12 samples available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

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

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 to adults with wet AMD was safe and generally well tolerated at doses ranging from $6x10^9$ to $3x10^{10}$ vg/eye through Week 36
  - No dose-limiting toxicities and no 4D-150–related serious adverse events
  - 14/15 participants experienced no intraocular inflammation
  - No hypotony
- Durable clinical activity demonstrated across all 4D-150 dose cohorts through Week 36
  - Up to 81% reduction in mean annualized anti-VEGF injection rate through Week 36
  - Stable BCVA and CST
- Enrollment in Phase 2 dose expansion (N=50) completed
  - 4D-150 ($1x10^{10}$ vg/eye or $3x10^{10}$ vg/eye) vs aflibercept 2 mg

Acknowledgments