Phase 2 Population Extension Cohort in the PRISM Clinical Trial Evaluating 4D-150 in Adults with Neovascular Age-related Macular Degeneration

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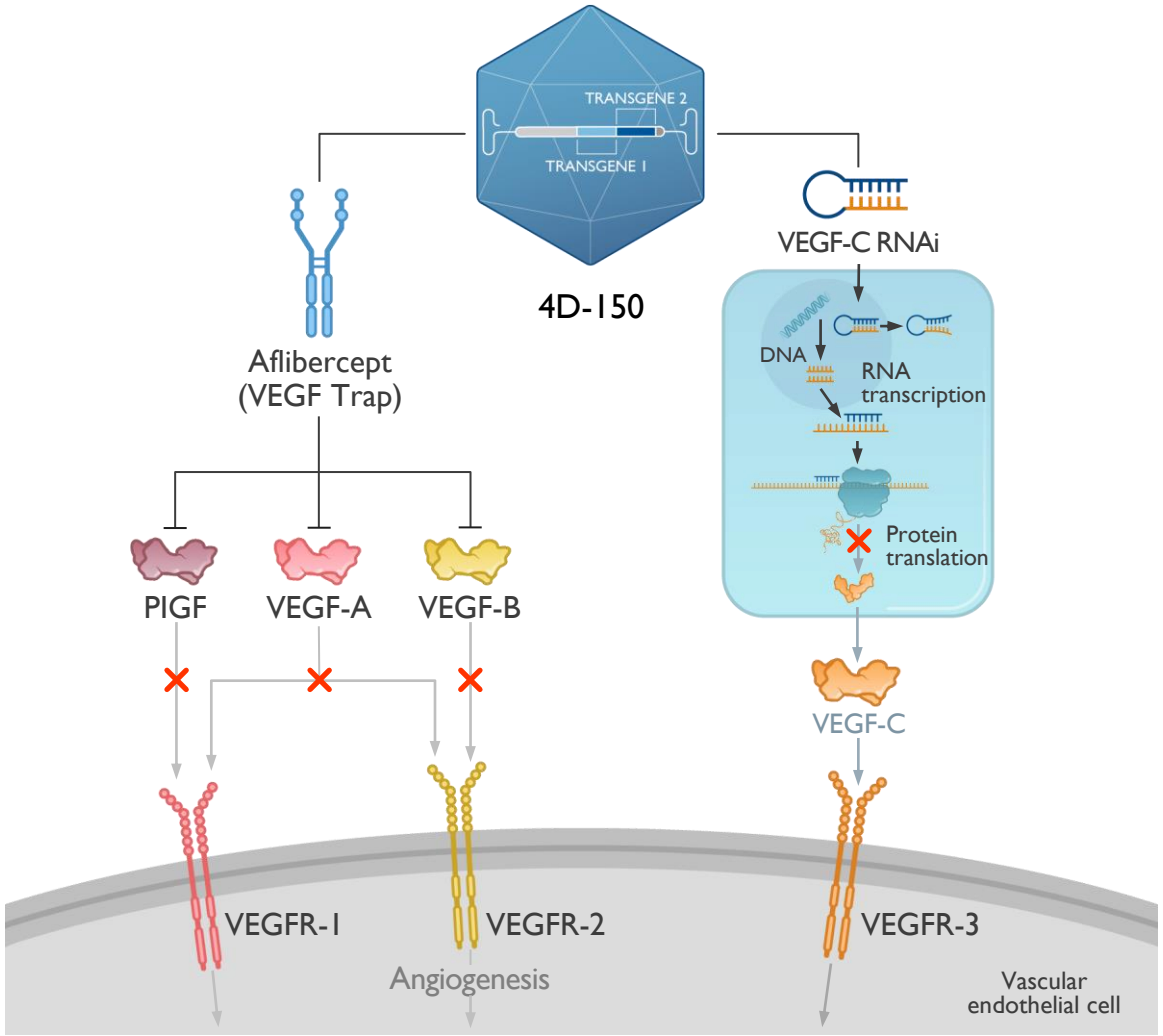
4D-150

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

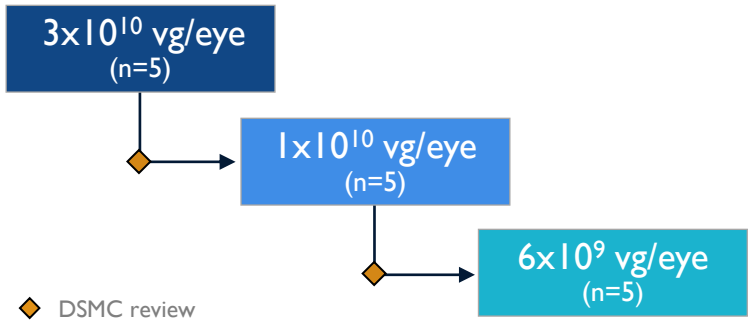


PlGF, placental growth factor; VEGF, vascular endothelial growth factor.

PRISM Phase 1/2 Study Design

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

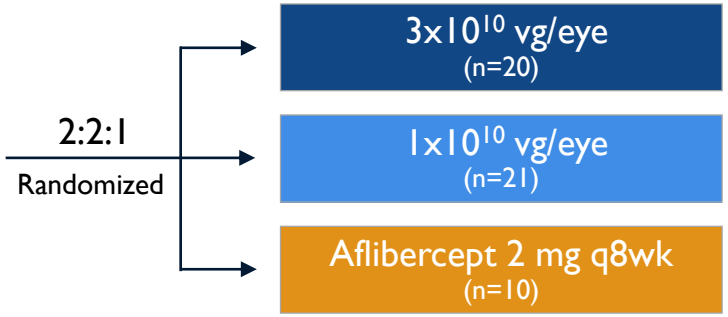
Phase 1 Dose Exploration



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

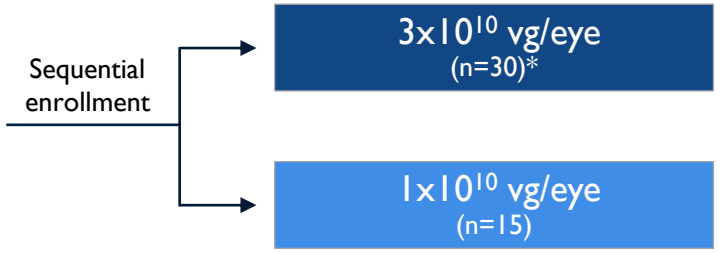
Phase 2 Dose Expansion



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

Phase 2 Population Extension



Key Inclusion Criteria

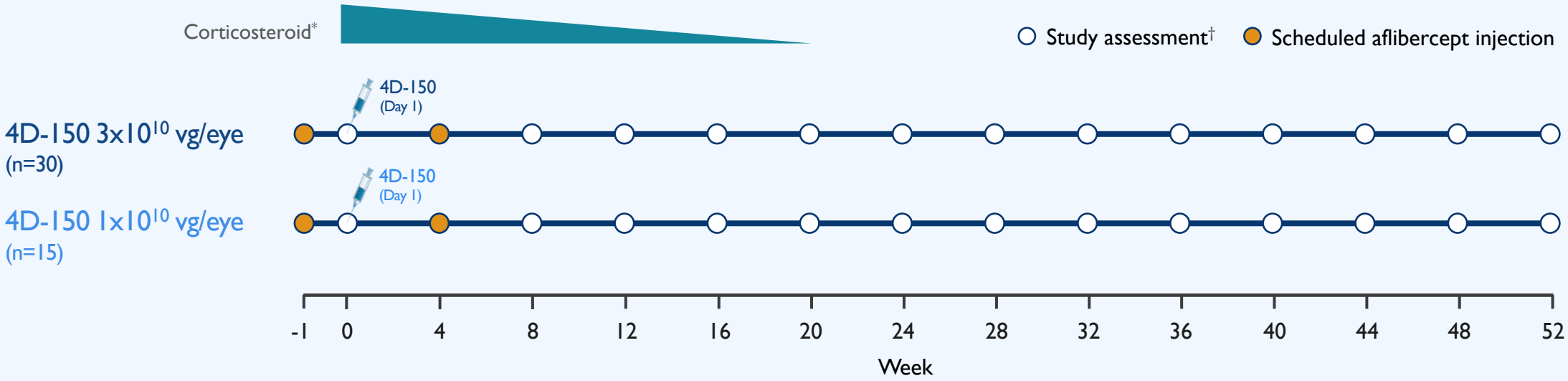
- Anti-VEGF injections in the prior 12 months: 1–6 (≥1 in last 12 wks)
- CST: No minimum
- BCVA: 34–83 ETDRS letters

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

PRISM Phase 2 Population Extension

Study Design

Phase 2 Population Extension



Key Endpoints

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

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

*Participants received one of the following: (a) difluprednate ophthalmic emulsion, (b) triamcinolone acetonide with prednisolone taper, or (c) dexamethasone . † Visual acuity, optical coherence tomography, ophthalmic exam.

Demographics and Baseline Characteristics

Population Extension Cohort

	3×10^{10} vg/eye (N=30)	1×10^{10} vg/eye (N=15)	Total (N=45)
Mean ±SD age, years	77 ±7.7	78 ±8.6	77 ±7.9
Female, n (%)	20 (67)	6 (40)	26 (58)
Race, n (%) White Asian	 30 (100) 0	 14 (93) 1 (7)	 44 (98) 1 (2)
Mean ±SD BCVA, ETDRS letters	71 ±9.9	73 ±8.8	72 ±9.5
Mean ±SD central subfield thickness, μm	336 ±135.0	314 ±70.8	329 ±117.1
Mean ±SD time since diagnosis, years	1.8 ±3.5	0.7 ±0.9	1.4 ±2.9
Mean ±SD *actual* anti-VEGF injections in prior 12 months*	4.4 ±2.0	4.3 ±2.1	4.4 ±2.0
Mean *annualized* injection rate, prior 12 months*	8.3	10.7	9.0

*Includes Day -7 aflibercept injection. BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation; VEGF, vascular endothelial growth factor.

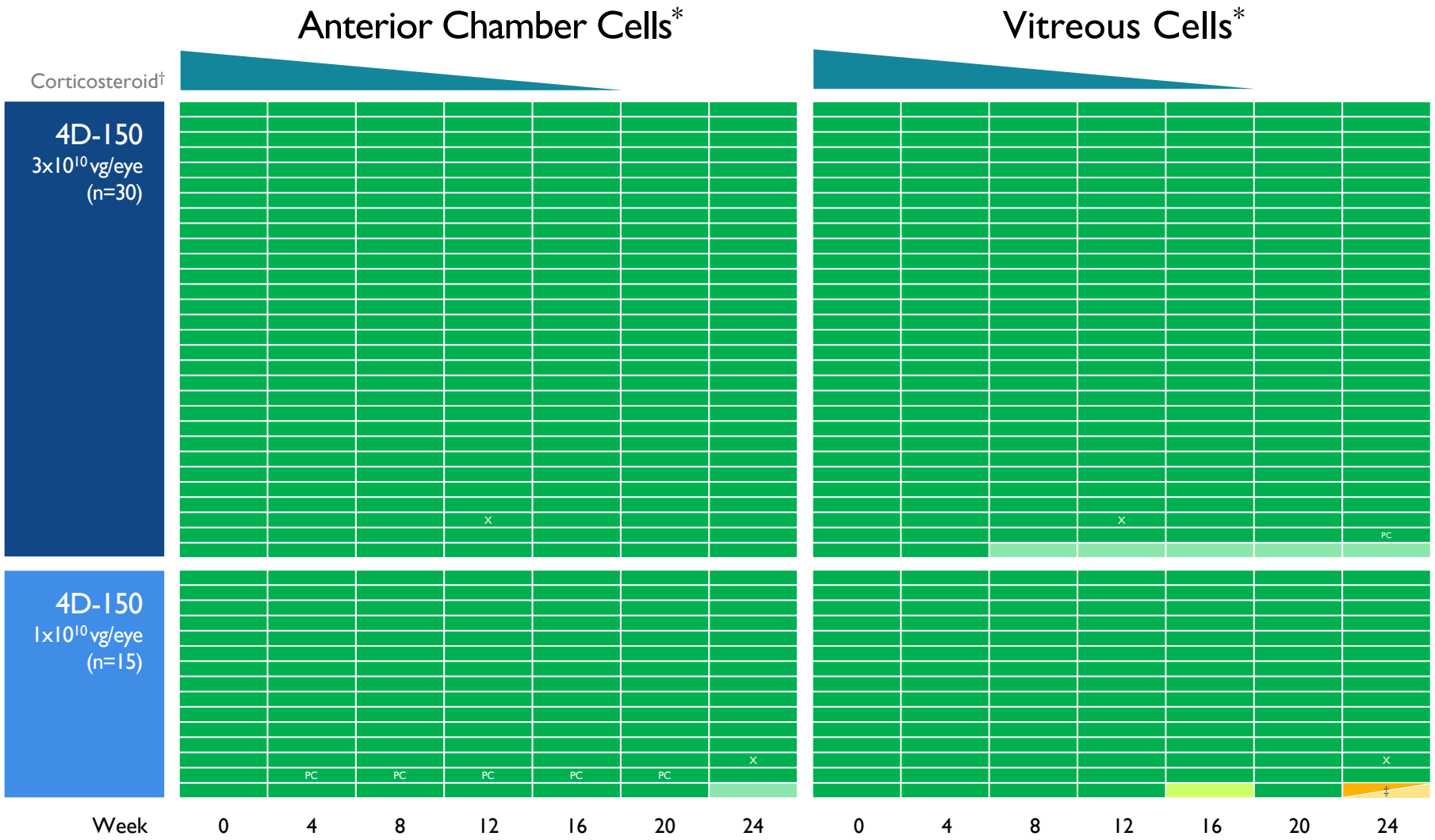
Safety and Tolerability

Interim Analysis (Week 24)

- 4D-150 was safe and generally well tolerated
- No 4D-150–related serious adverse events
- No hypotony, endophthalmitis, retinal vasculitis, choroidal effusions, or retinal artery occlusions
- Intraocular inflammation analysis:
  - 1×10^{10} vg/eye: moderate vitritis (n=1 of 15)
  - 3×10^{10} vg/eye: mild vitreal cells (n=1 of 30); no additional steroids

Ophthalmic Examination

Population Extension Cohort (Week 24)

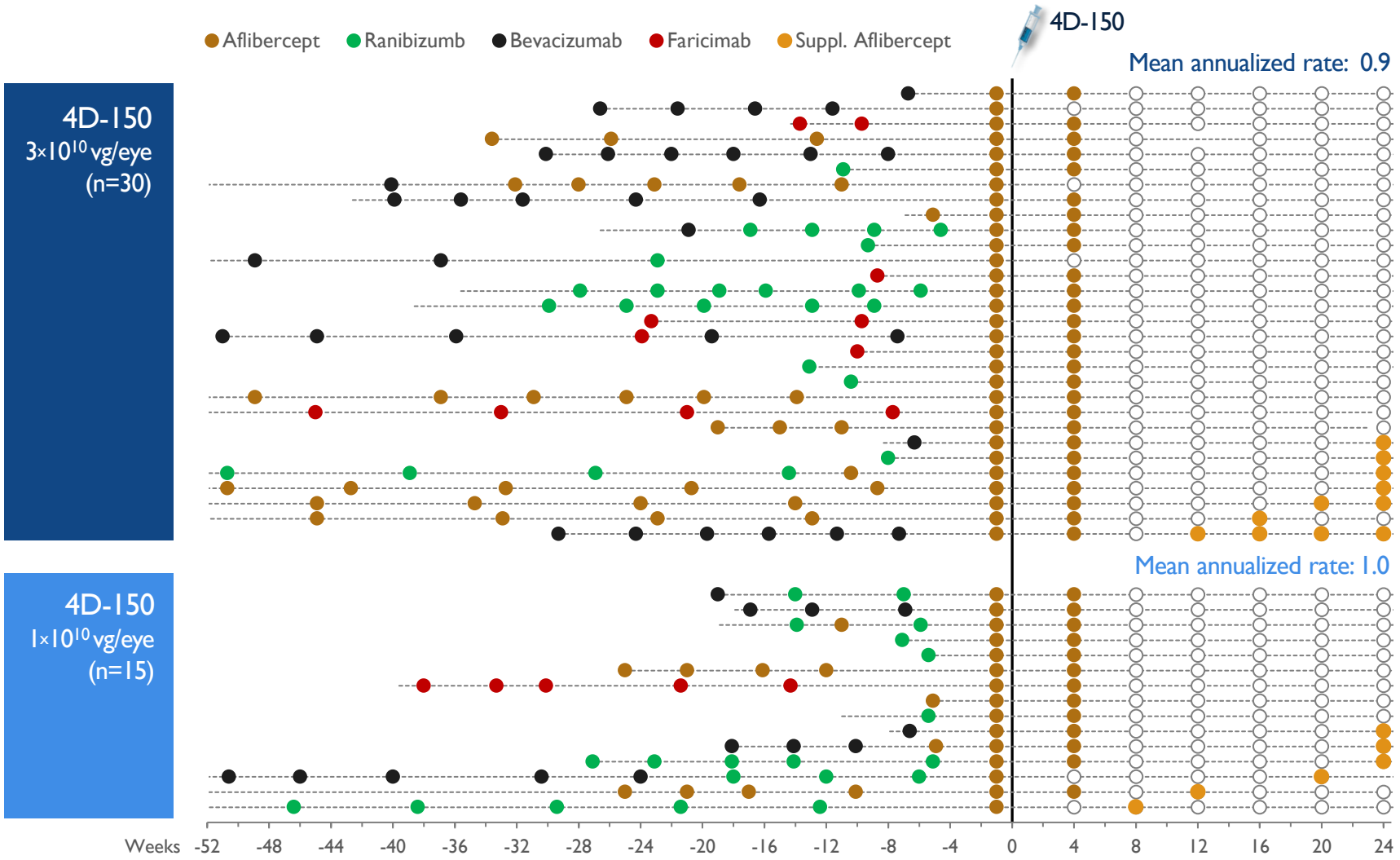


- $3x10^{10}$ vg/eye:
  - 30/30 completed steroid regimen on schedule
  - 0/30 restarted
- $1x10^{10}$ vg/eye:
  - 13/15 completed steroid regimen on schedule
  - 2/15 on steroids at week 24 (1 restarted)

*SUN and NEI Scores for white blood cells. †Either difluprednate ophthalmic emulsion, triamcinolone acetonide with prednisolone taper, or dexamethasone. ‡Assessed as 2+ by primary investigator one day after initial assessment as 3+ by sub-investigator; 1+ vitreous cells observed in the contralateral eye; participant had a history of syphilis (reportedly treated). NEI, National Eye Institute; PC, pigmented cells; SUN, Standardization of Uveitis Nomenclature; X=missed visit.

Anti-VEGF Injections (Week 24)

Up to 91% Reduction in Annualized Anti-VEGF Injection Rate



Post Week 4*

89% reduction in annualized anti-VEGF injection rate

93% ≤1 injection

77% injection-free

91% reduction in annualized anti-VEGF injection rate

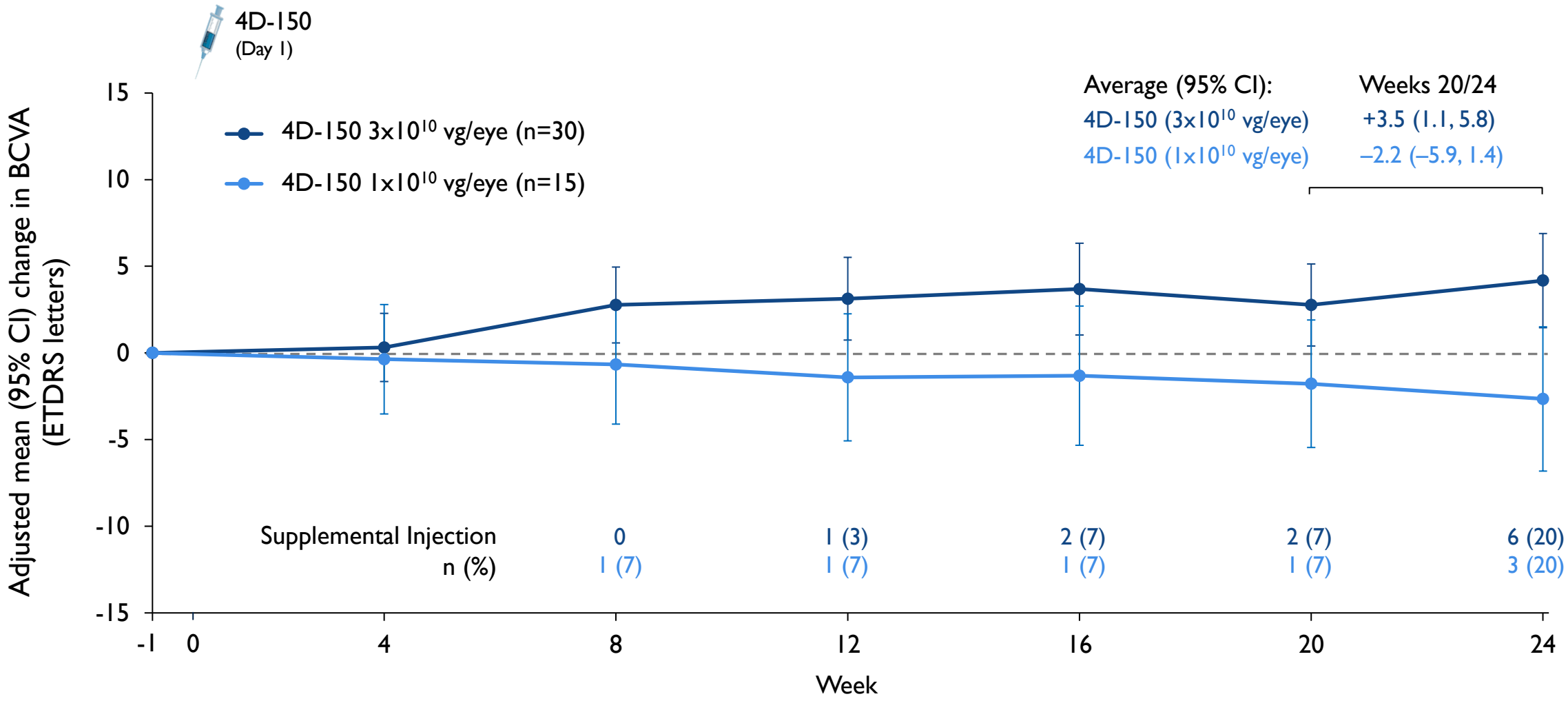
100% ≤1 injection

60% injection-free

Data cutoff, 24 June 2024. *Scheduled on-study aflibercept injection administered at Week 4.

Best Corrected Visual Acuity (BCVA)

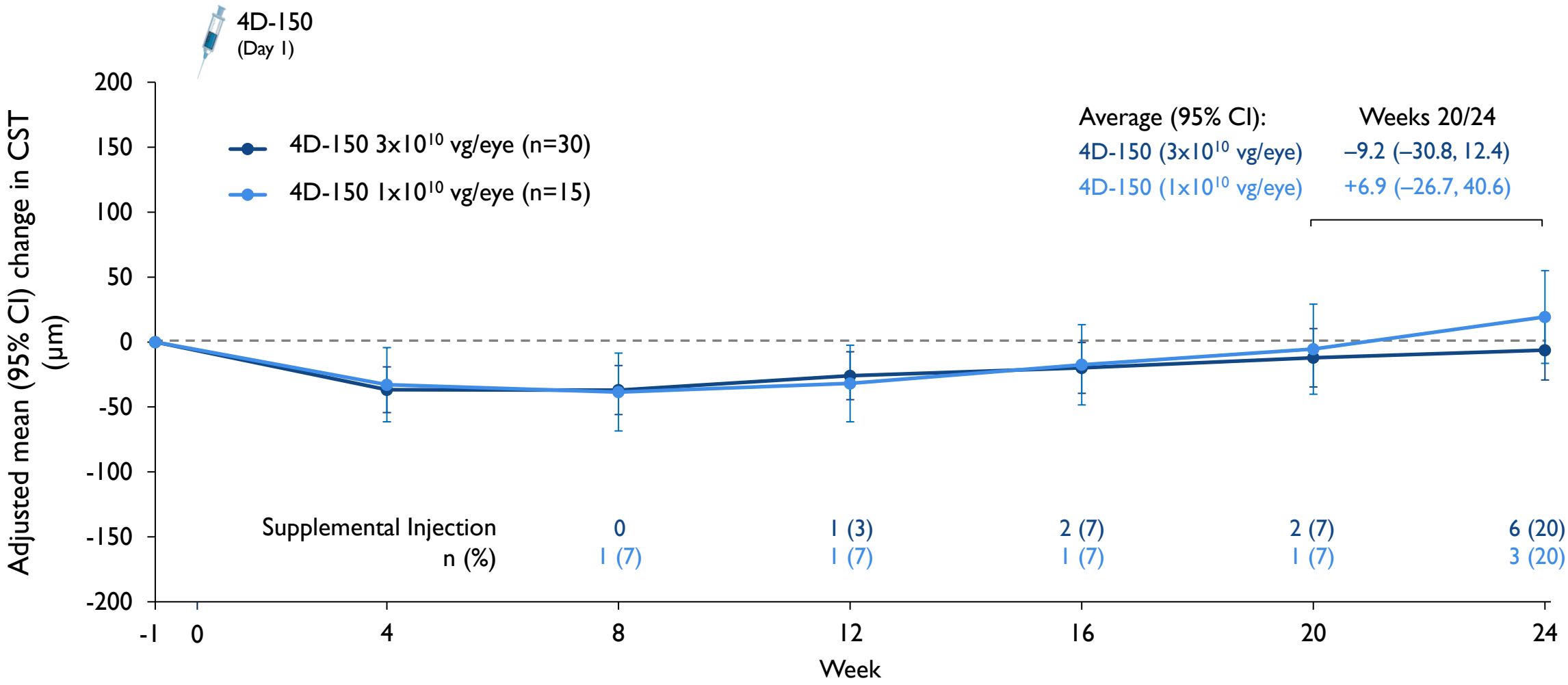
3x10^{10} vg/eye: Durable Improvement in Visual Acuity Through Week 24



Data cutoff, 24 June 2024. 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.
CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study.

Central Subfield Thickness (CST)

3x10[10] vg/eye: Stable Anatomic Control Through Week 24

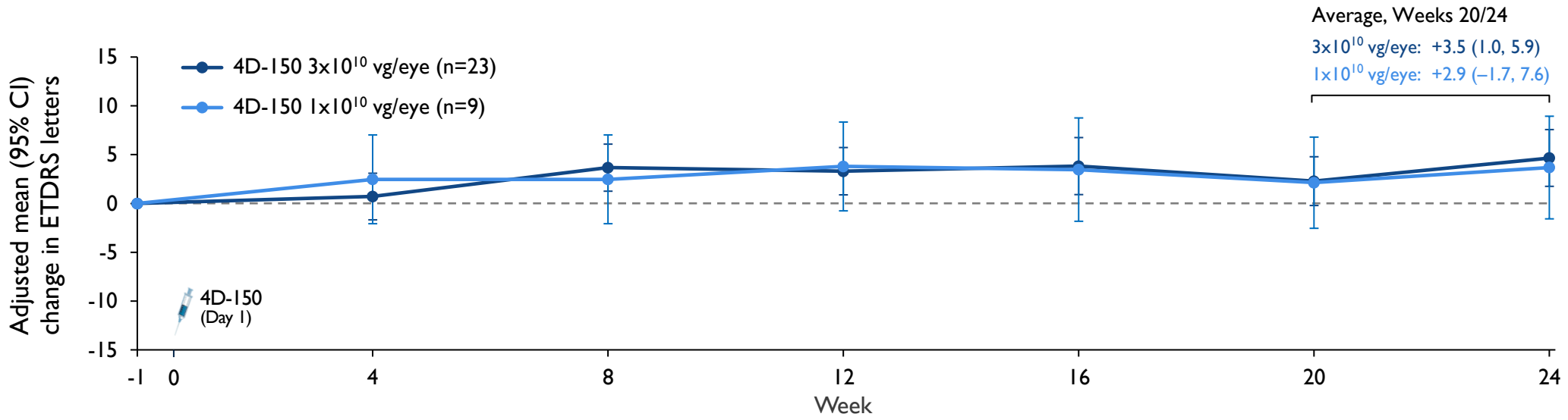


Data cutoff, 24 June 2024. Adjusted mean and 95% CI estimated from a mixed–effect model for repeated measures including observed data (weeks 4-24) without imputing missing values. CI, confidence interval.

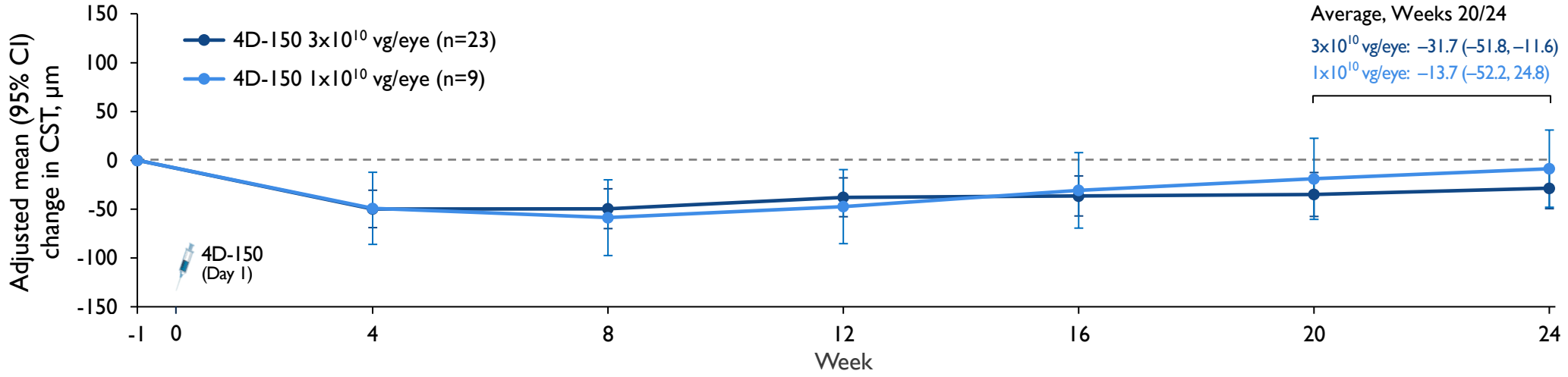
Supplemental Injection-free Participants

$3x10^{10}$ vg/eye: Durable Improvement in Visual Acuity and Sustained Reduction in CST

BCVA



CST



Data cutoff, 24 June 2024. 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; CI, confidence interval; CST, central retina thickness; ETDRS, Early Treatment Diabetic Retinopathy Study.

Summary and Conclusions

- 4D-150 was safe and well tolerated through 24 weeks in individuals with wAMD and moderate disease activity
  - No 4D-150–related SAEs
  - No hypotony, endophthalmitis, retinal vasculitis, choroidal effusions, or retinal artery occlusions
  - 3×10^{10} vg/eye: 30/30 completed prophylactic steroids on schedule, none restarted
- 89–91% reduction in mean annualized anti-VEGF injection rate
- 4D-150 3×10^{10} vg/eye
  - 77% supplemental injection-free, 93% ≤1 supplemental injection
  - Durable improvement in BCVA
  - Stable CST
- Initiation of Phase 3 program anticipated in early 2025

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