Extended Follow-Up in the PRISM Clinical Trial Evaluating 4D-150 in Adults with Neovascular Age-related Macular Degeneration

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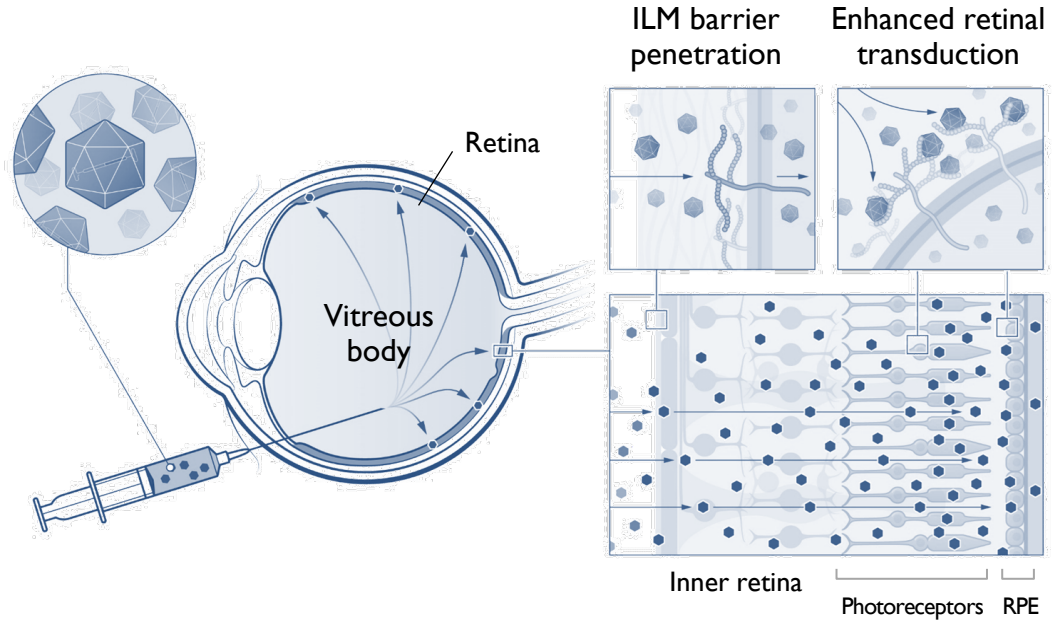
4D-150: R100-based Intravitreal Genetic Medicine

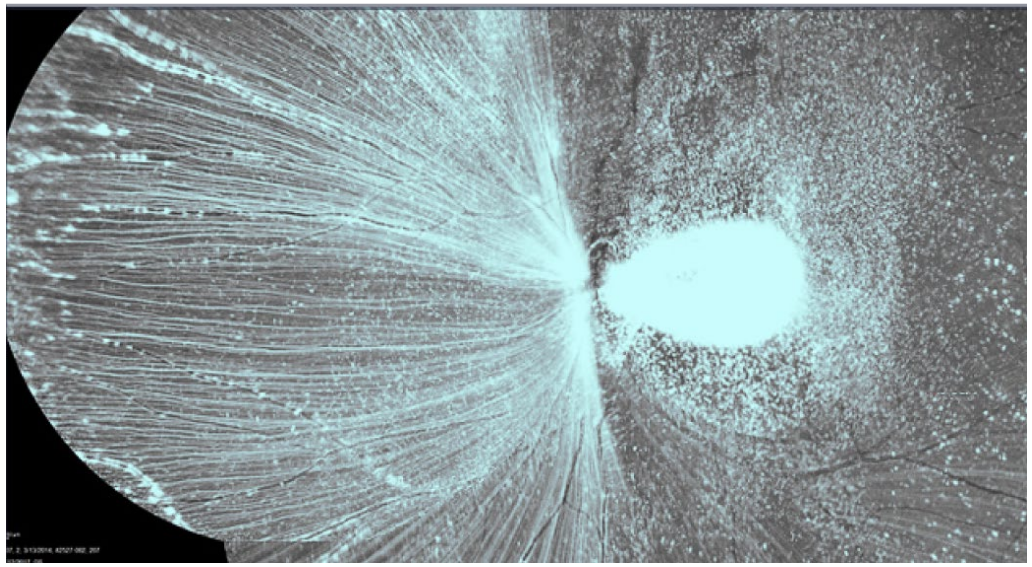
Retinotropic 100 Vector is Optimized to Penetrate ILM and Transduce All Layers of the Retina

R100: Evolved AAV Vector



- Synthetic AAV capsid variant with enhanced capacity to penetrate vitreoretinal barriers

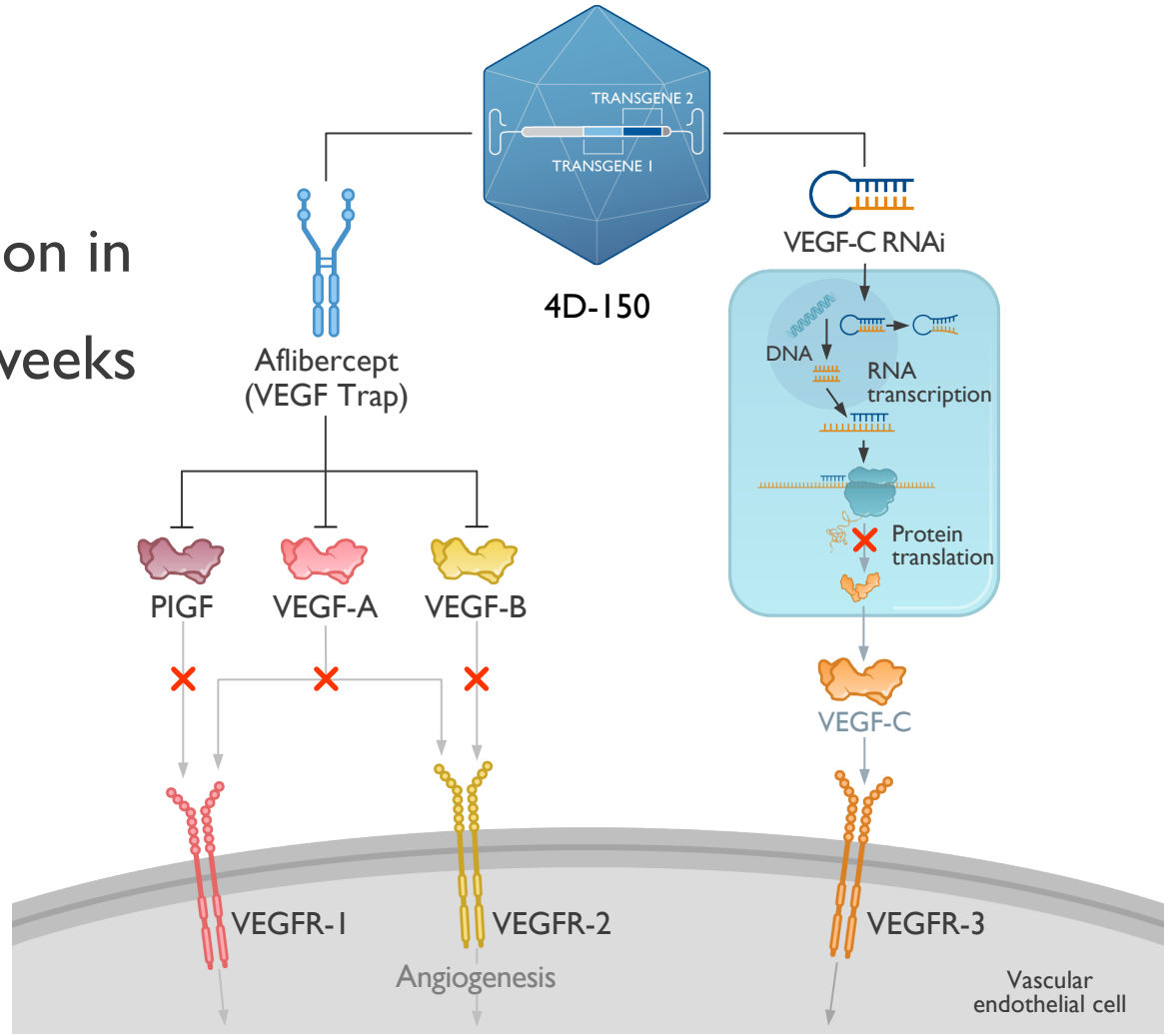
EGFP Expression in Primate Retina Following IVT Injection of R100.EGRP



AAV, adeno-associated vector; IVT, intravitreal; PlGF, placental growth factor; VEGF, vascular endothelial growth factor.

4D-150 is designed to deliver a dual-transgene payload of aflibercept & VEGF-C RNAi Expression

- Steady state expression in approximately 8-12 weeks

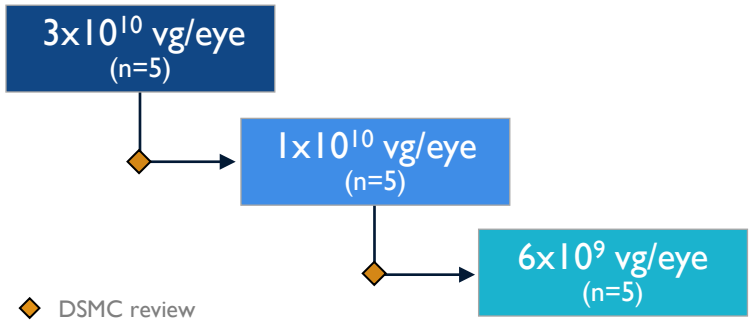


PIGF, placental growth factor; VEGF, vascular endothelial growth factor.

PRISM Study Design

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

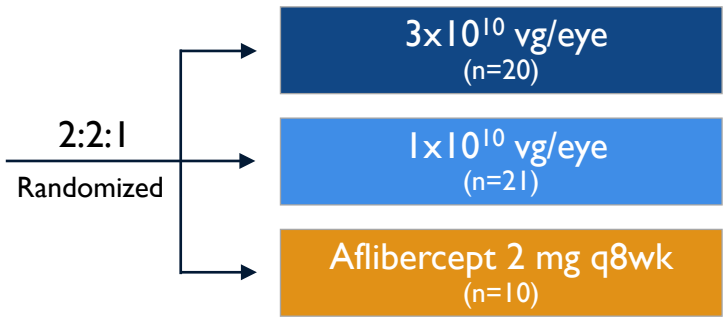
Phase 1 Dose Exploration



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

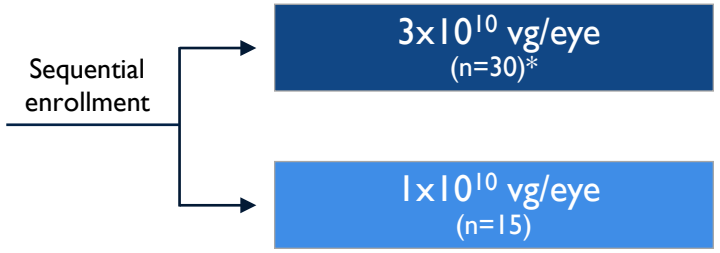
Phase 2a Dose Expansion



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

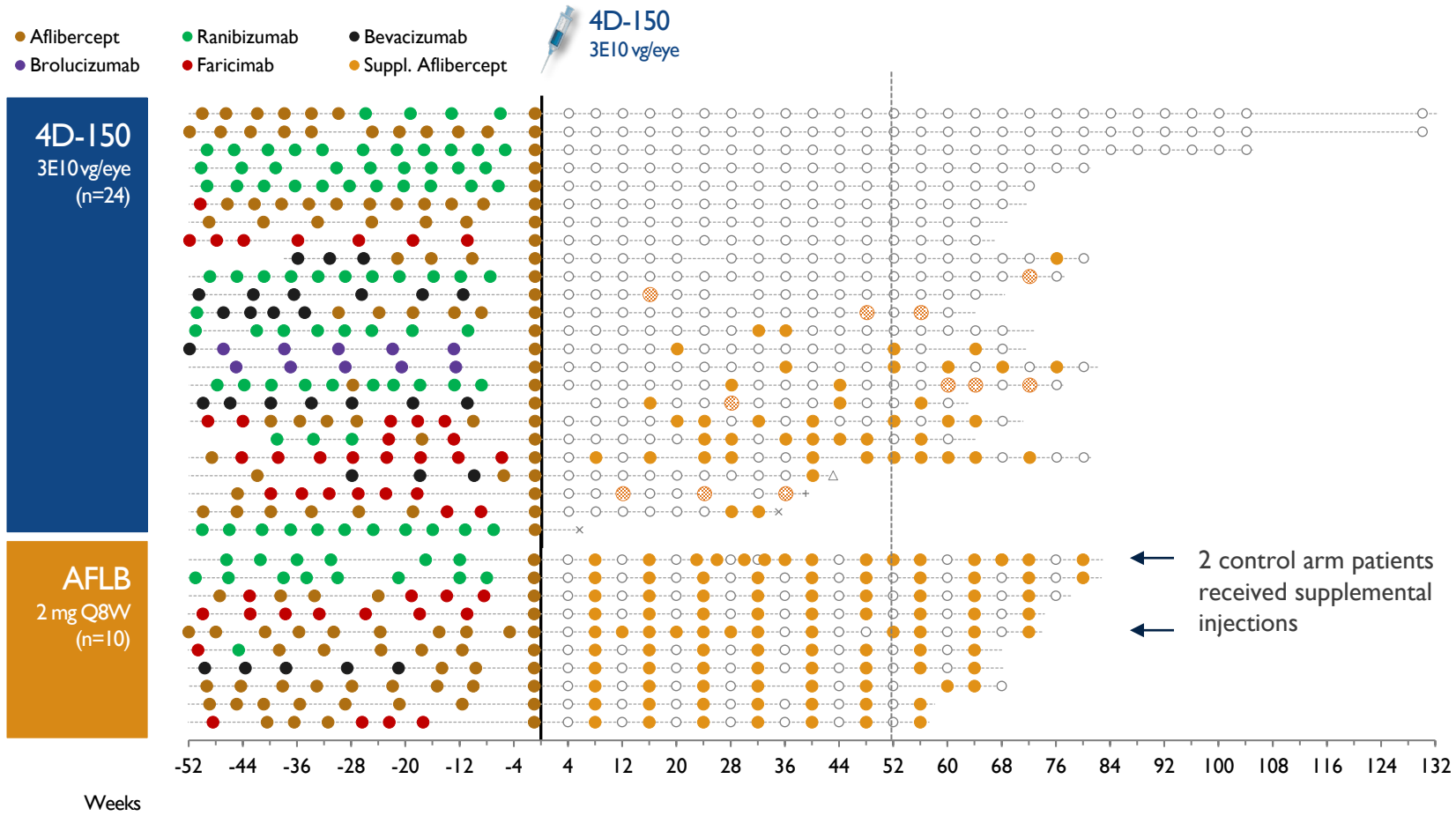
*Includes participants in the alternative steroid cohort who enrolled under the Population Extension eligibility criteria (n=13).

4D-150 PRISM Development Program
Started with the Most Severe and Moved to a Broad Patient Population

PRISM	Phase 1 "Severe" 3E10 vg/eye (N=5)	Phase 2a "Severe" 3E10 vg/eye (N=20)	Phase 2a "Severe" Aflibercept 2mg Q8W (N=10)	Phase 2b "Broad" 3E10 vg/eye (N=30)
Age, years (Mean ±SD)	79 ±8.7	77 ±8.0	80 ± 4.1	77 ±7.7
BCVA, ETDRS letters				
Mean ±SD	55 ±16.6	68 ±11.3	71 ±13.2	71 ±9.9
Range	*28–73*	*35–80*	*43–87*	*45–83*
CST (central subfield thickness), µm				
Mean ±SD	424 ±99.2	429 ±89.3	419 ±64.3	336 ±135.0
Range	*302–505*	*319–742*	*326–521*	*188–702*
Time since diagnosis, years				
Mean ±SD	2.2 ±1.7	4.0 ±3.0	2.1 ±1.5	1.8 ±3.4
Range	*1.0–5.1*	*0.7–11.1*	*1.0–5.7*	*0.1–13.9*
Recently Diagnosed*, N= (%)	0 (0%)	0 (0%)	0 (0%)	16 (53%)
Actual anti-VEGF injections in prior 12 mo†				
Mean ±SD	11.4 ±2.6	9.9 ±2.4	9.3 ±0.9	4.4 ±2.0
Range	*7–13*	*7–13*	*8–11*	*2–7*

*Defined as ≤6 months since diagnosis at screening. †Includes Day -7 aflibercept injection. BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation; VEGF, vascular endothelial growth factor.

Phase 1/2a: >80% Reduction in Annualized Anti-VEGF Injections at Week 52 in Severe Disease Cohorts (3E10 vg/eye)



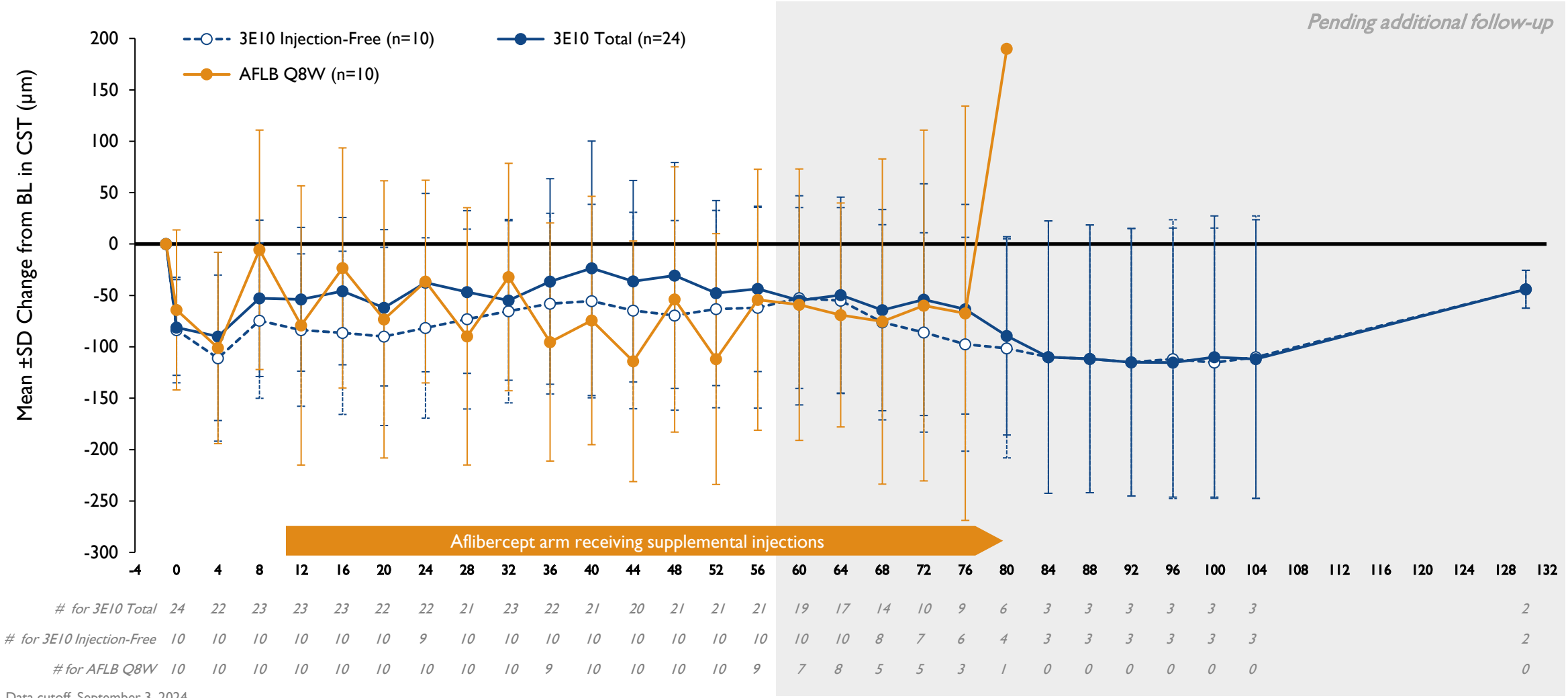
Anti-VEGF Injections (Week 52)

Study Population	Annualized Reduction	Supplemental Injections*		
		0–2	0–1	0
Phase 1/2a (N=24)	**83%**	**73%**	**52%**	**44%**
Phase 1 (N=4)	**91%**	**75%**	75%	75%
Phase 2a (N=20)	**81%**	**73%**	47%	37%
AFLB Q8W (n=10)	28%	NA	NA	NA

*Kaplan-Meier estimates

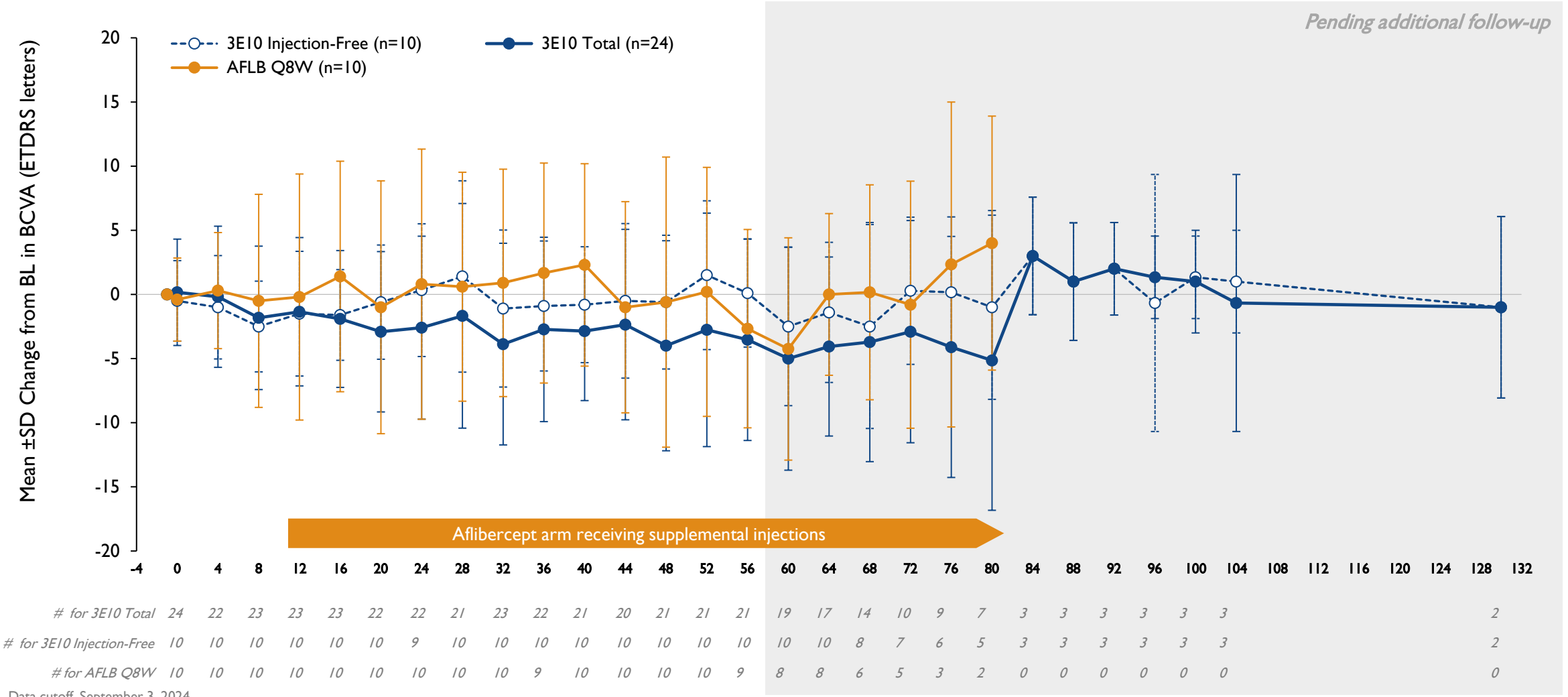
⊗ Supplemental injection administered based on investigator discretion (protocol-defined visual and anatomic criteria not met).
+ Participant censored for supplemental injection assessment owing to protocol deviation (lost to follow up for >3 months after entering a nursing home).
X Early termination (death unrelated to study treatment), one of whom had missing data from Week 36 until death at Week 57.
Δ Subretinal macular hemorrhage at Week 41; PI elected to administer 5 consecutive doses of aflibercept (4-week dosing interval) while blood resorbed (i.e., no new/ongoing hemorrhage); all 5 aflibercept injections were included in the calculation of mean annualized anti-VEGF injections. PI subsequently converted to an 8-week aflibercept dosing schedule; however, criteria for supplemental injection were not present. At week 104, the mean change from baseline in BCVA was -1 letter and the mean change in CST was -71 μm.
Data cutoff, September 3, 2024.

Phase 1/2a (4D-150 3E10 vg/eye): Sustained Anatomic Control



Data cutoff, September 3, 2024.

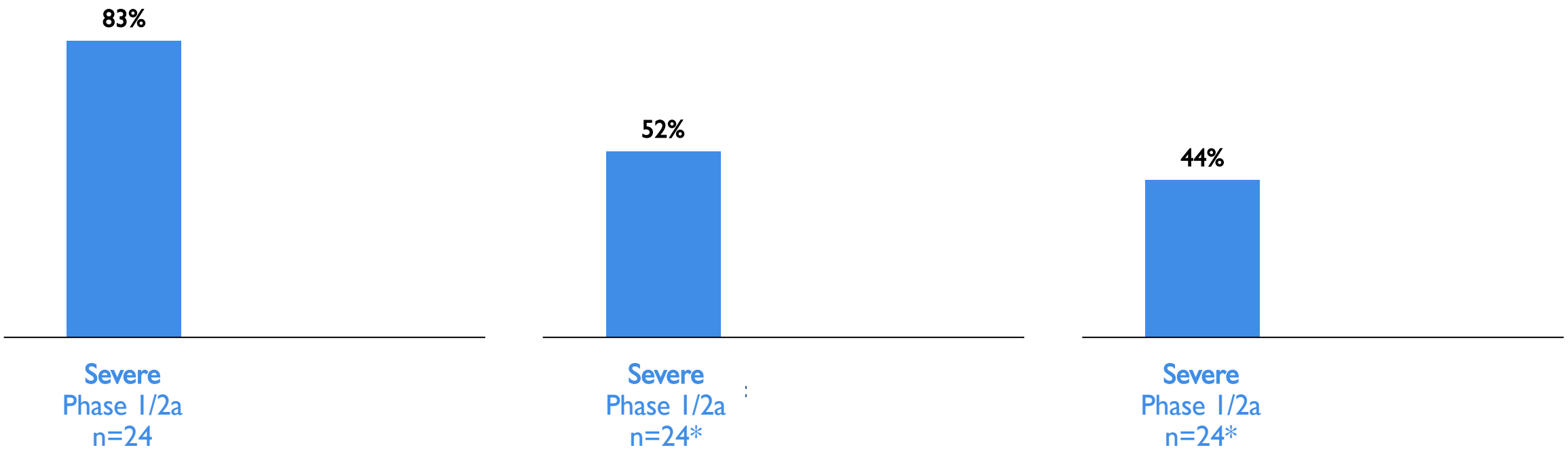
Phase 1/2a (4D-150 3E10 vg/eye): Comparable Visual Acuity AFLB 2Q8



Data cutoff, September 3, 2024.

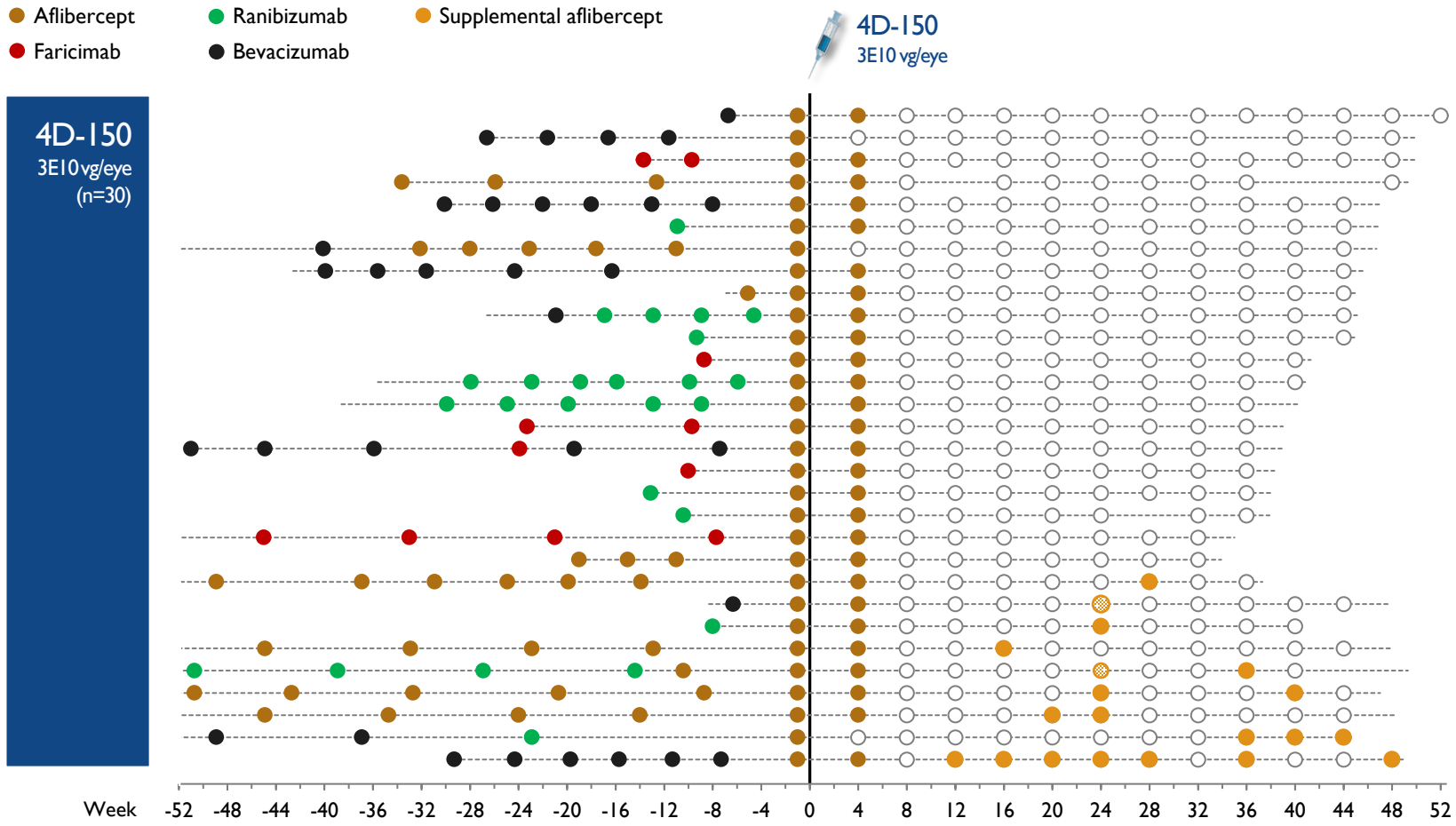
Reduction in Treatment Burden in Severe Wet AMD Patients Through 52 Weeks (Phase 3 Dose: 3E10 vg/eye)

% Reduction in Annualized Injections	% 0–1 Supplemental Injections	% Supplemental Injection-free



Data cutoff, September 3, 2024.
*Based on Kaplan-Meier method for calculating endpoint with follow-up through 52 weeks (Phase 1/2a).

Phase 2b (3E10 vg/eye): 70% Injection-free Over 52 Week Follow-up (Kaplan-Meier Estimate)



Supplemental Injections*

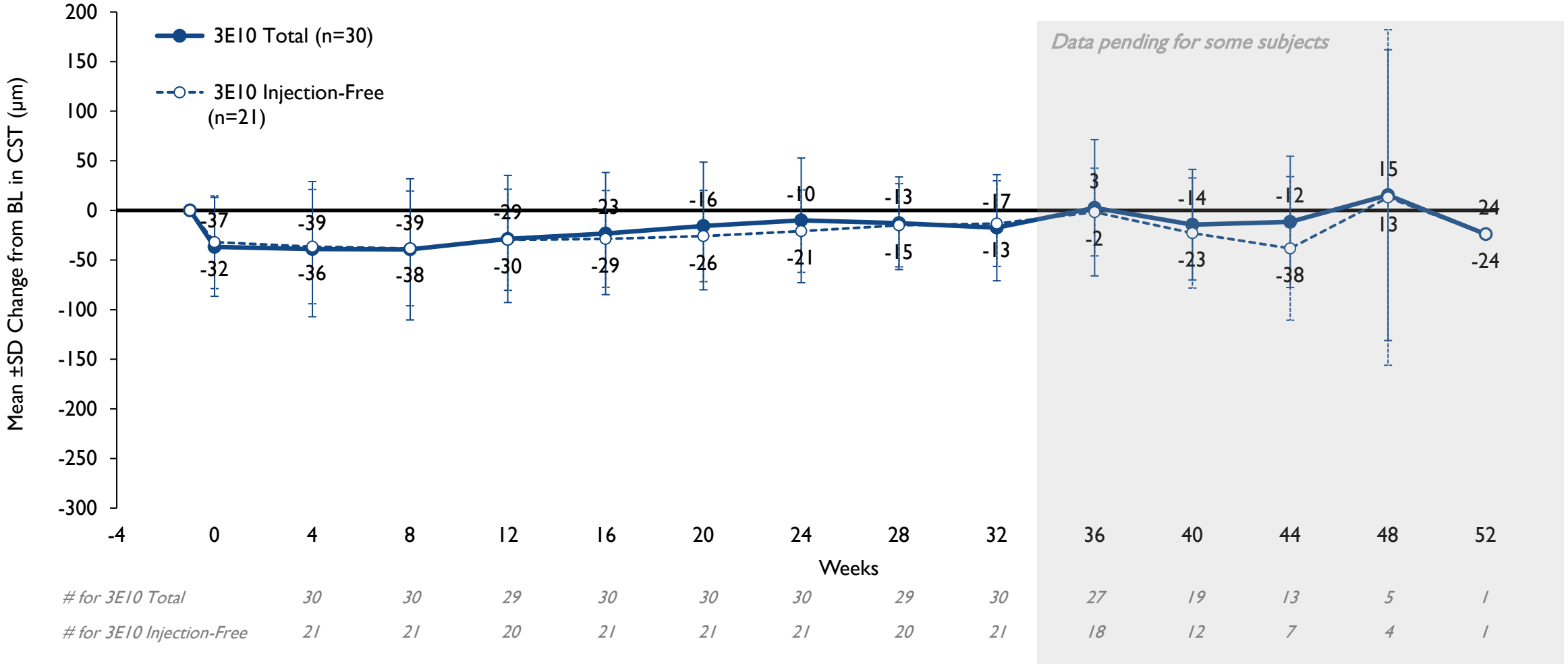
Status	Week 32	Week 52
Injection-free	73%	70%
0-1 injection	93%	80%

*Kaplan-Meier estimates

Data cutoff, September 3, 2024.

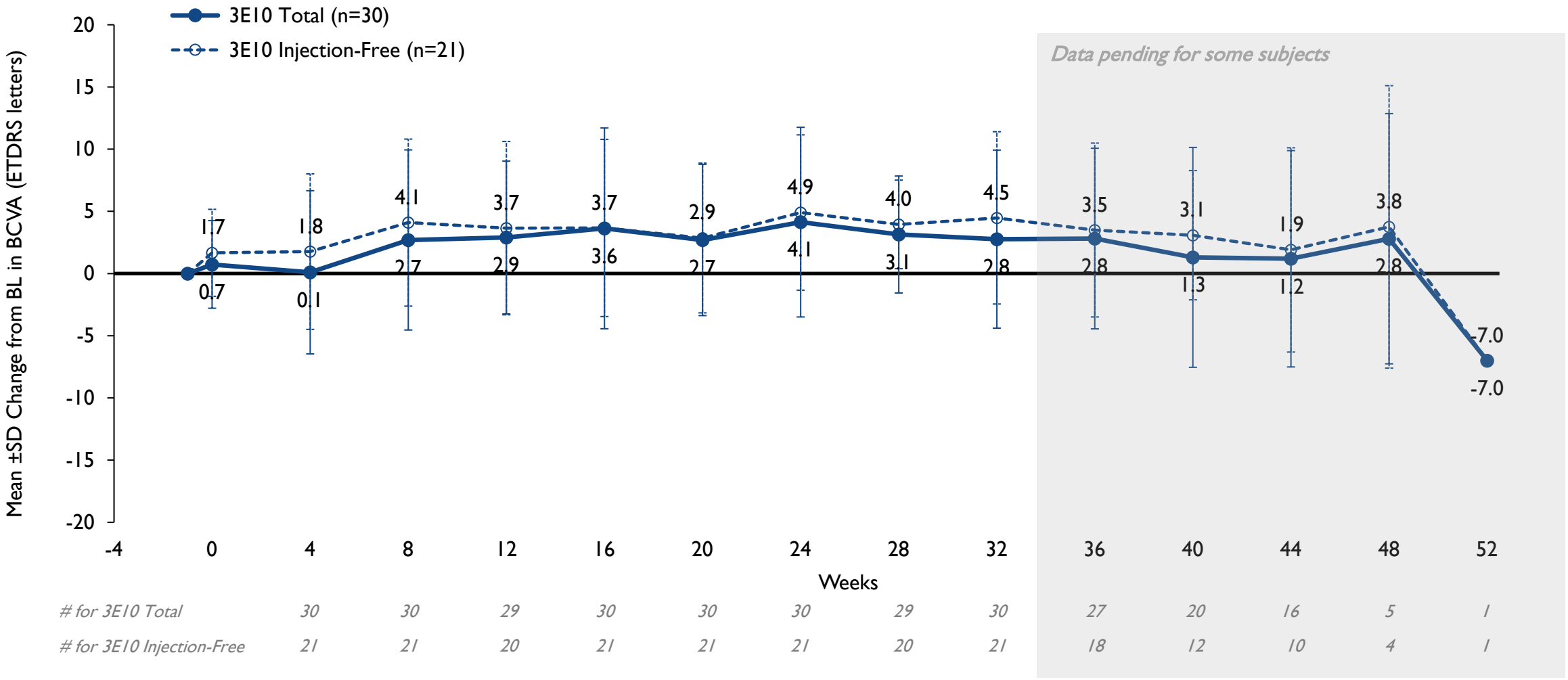
Supplemental injection administered based on investigator discretion (protocol-defined visual and anatomic criteria not met).

Phase 2b: Sustained Anatomic Control



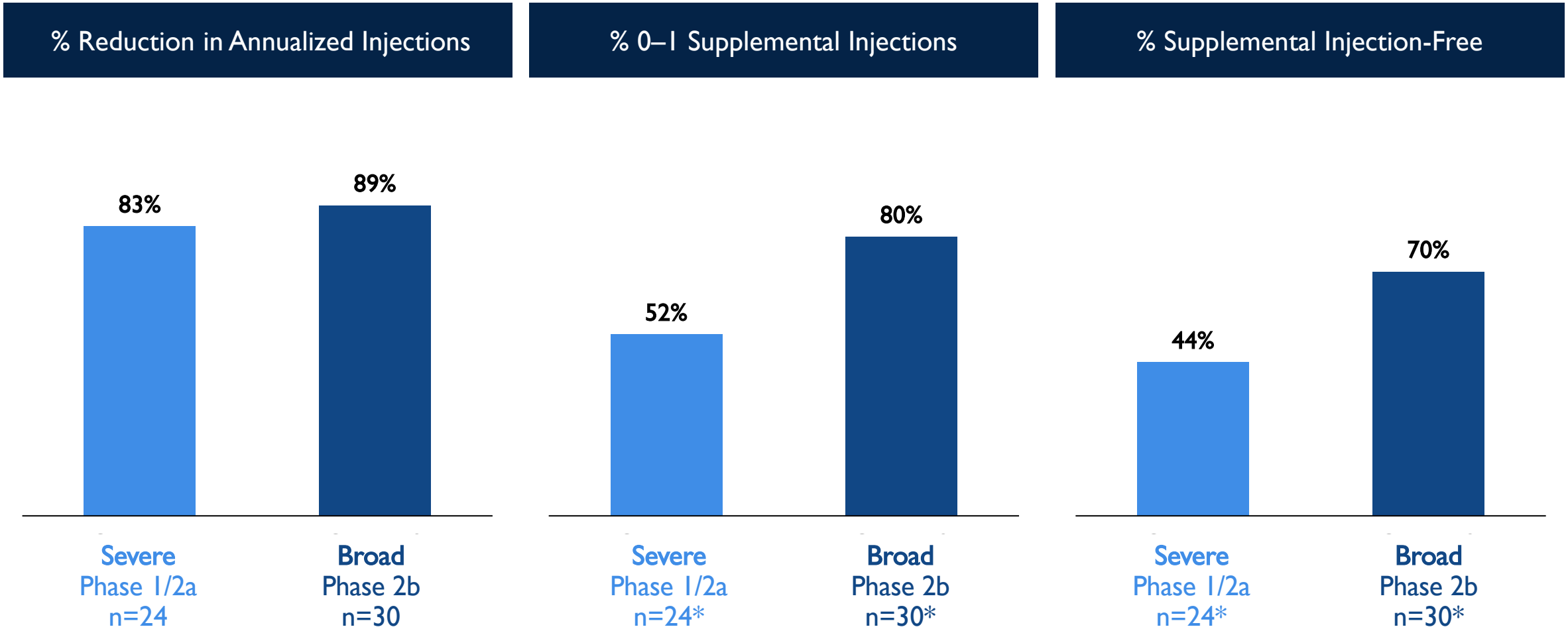
Data cutoff, September 3, 2024.

Phase 2b: Visual Acuity Improved and Stable



Data cutoff, September 3, 2024.

Treatment Burden in Broad Wet AMD Population **Through 52 Weeks** (Phase 3 Dose: 3E10 vg/eye)



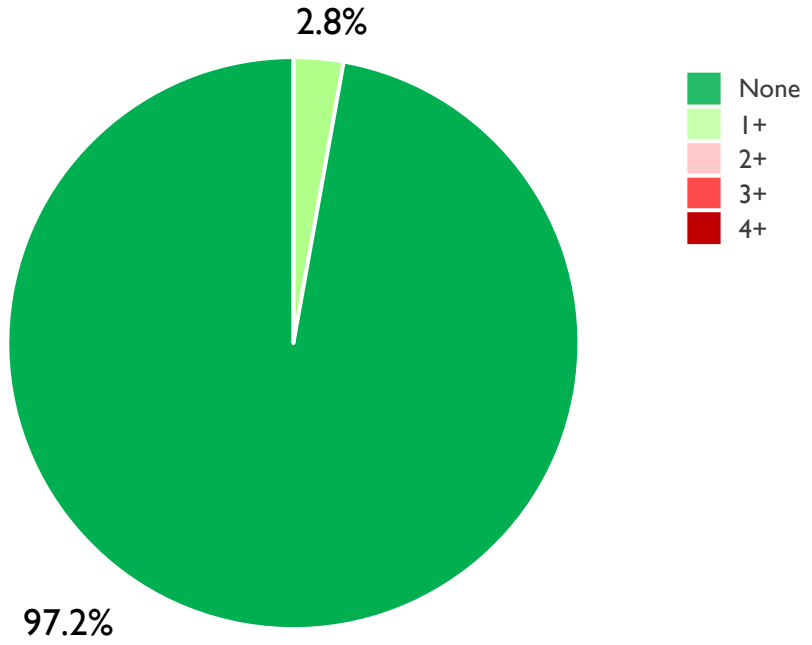
Data cutoff, September 3, 2024.
*Based on Kaplan-Meier method for calculating endpoint with variable follow-up through 32-52 weeks.

4D-150 Safety

- No 4D-150–related serious adverse events
- Rate of 3E10 dose 4D-150–related intraocular inflammation: **Wet AMD**
  - **2.8%** (2 of 71) had transient 1+VC at any timepoint
  - **99%** (70 of 71) completed steroid prophylaxis taper on schedule
  - **97%** (69 of 71) remained off steroids completely
- No 4D-150–related hypotony, endophthalmitis, vasculitis, choroidal effusions or retinal artery occlusions observed to date
  - Supplemental aflibercept injection-related case of endophthalmitis (presumed bacterial infection), resolved over following 2 visits
- Rate of 4D-150–related intraocular inflammation: **DME**
  - **0%** treated at any dose (n=22) had IOI at any timepoint

All 4D-150 3E10 vg/eye-Treated Wet AMD Patients (N=71)

*Highest SUN/NEI Score (4D-150–Related)**

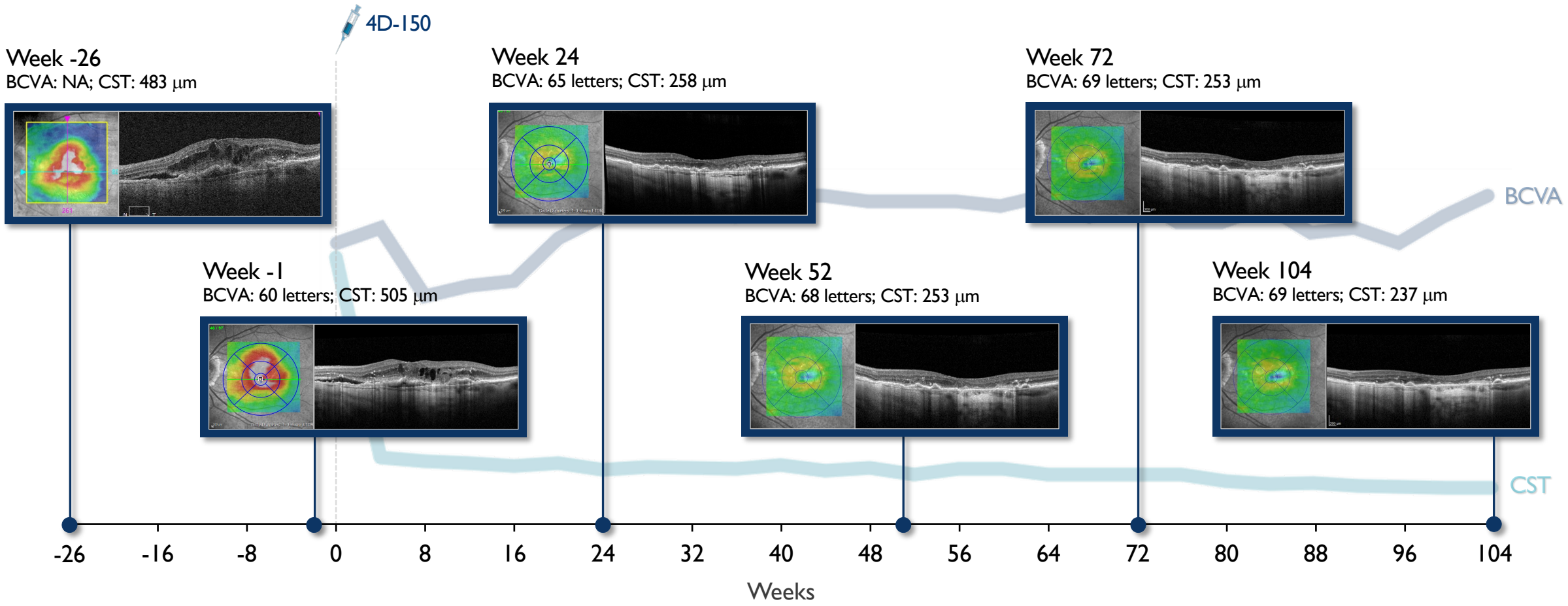


Data cutoff, August 23, 2024.
*Duration of follow up, ≤2.5 years. NEI, National Eye Institute; SUN, Standardization of Uveitis Nomenclature.

Case Study: Phase 1 (3E10 vg/eye)

89-year-old female (13 anti-VEGF injections during prior 12 months)*

Sustained Improvement in BCVA & CST While Supplemental Injection-free at 2 Years



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

Key Takeaways

PRISM

Extended Follow-Up

TREATMENT BURDEN REDUCTION SEEN IN PRE-TREATED WET AMD PATIENTS

- ✓ Phase 1/2a – Severe disease with heavy pre-treatment
  - **83%** reduction in injection burden at 52-weeks compared to year prior to enrollment
  - **44%** of patients remain injection-free at 52-weeks post 4D-150 administration
- ✓ Phase 2b – Broad population
  - **70%** of patients remain injection-free at 52-weeks post 4D-150 administration
  - **80%** of patients needed 0-1 injection over 52-weeks post 4D-150 administration

SUSTAINED CONTROL OF ANATOMY AND VISUAL ACUITY SEEN ACROSS ALL POPULATIONS

SAFE & WELL TOLERATED, INCLUDING PHASE 3 DOSE (3E10)

- ✓ **2.8%** 4D-150 related IOI
- ✓ No 4D-150–related hypotony, endophthalmitis, vasculitis, choroidal effusions or retinal artery occlusions observed to date
- ✓ **99%** completed local steroid prophylactic regimen on schedule

Data cutoff date, August 26, 2024.

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