PRISM

Phase 2b Population Extension Cohort Evaluating 4D-150 in Neovascular Age-Related Macular Degeneration: 52-Week Results

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Disclosures

- **Consultant/Advisor:** Genentech, Regeneron, **4DMT,** Unity, Adverum, Perceive, EyePoint, Retina AI, Samsung, Neurotech, Opthea
- **Research Funding:** Genentech, Regeneron, REGENXBIO, **4DMT,** Unity, Adverum, Novartis, EyePoint, Ocular, Opthea, Janssen, Kodiak, Boehringer Ingelheim, Alimera, Apellis, Outlook, EyeBio/Merck, Oculis, Annexon

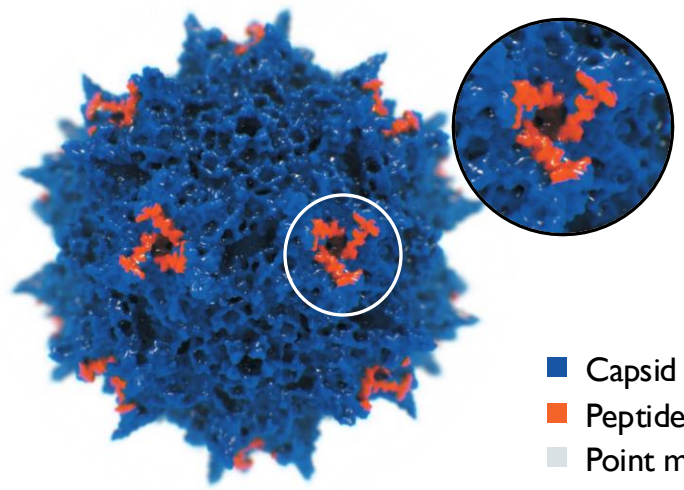
PRISM Phase 2b Clinical Trial: 52-Week Results

Take Home Points

- Improved visual acuity
- Sustained anatomical control
- Robust reduction in anti-VEGF injection burden
  - Overall Phase 2b population (3×10^{10} vg/eye): ~83% reduction vs projected on-label aflibercept Q8W
  - Recently diagnosed (3×10^{10} vg/eye): ~94% reduction vs projected on-label aflibercept Q8W
- 4D-150 was well tolerated
  - No significant IOI
  - No 4D-150–related serious adverse events
  - No 4D-150–related hypotony, endophthalmitis, occlusive/non-occlusive retinal vasculitis, choroidal effusions
- Initiation of Phase 3 program anticipated in early 2025

4D-150: Proprietary Capsid Carrying a Dual-Transgene Payload

R100 AAV Capsid



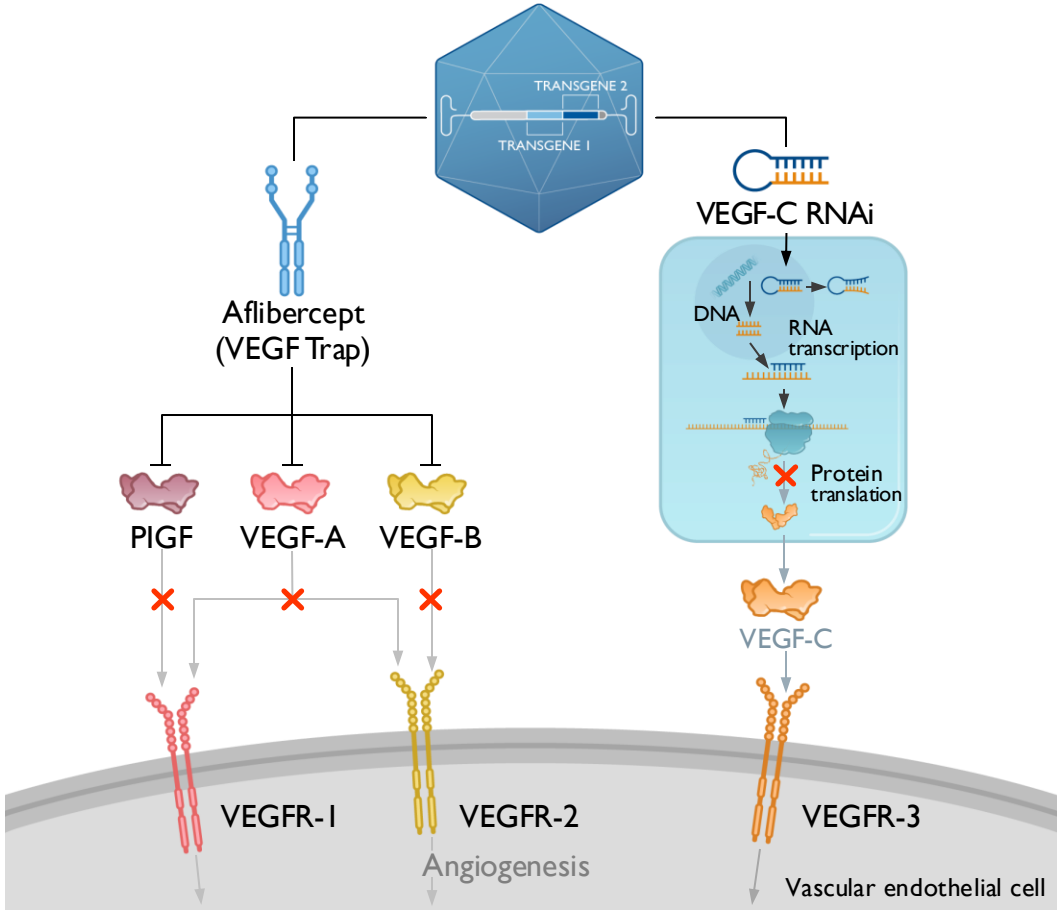
R100 capsid designed for:

Selective tropism for retinal cells

Efficient, low-dose gene delivery with no significant inflammation

Administration via routine intravitreal injection

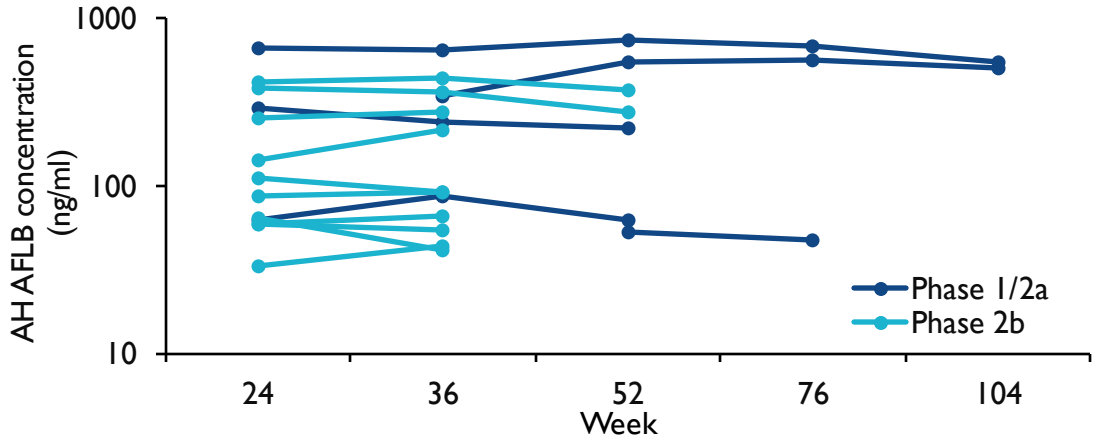
4D-150



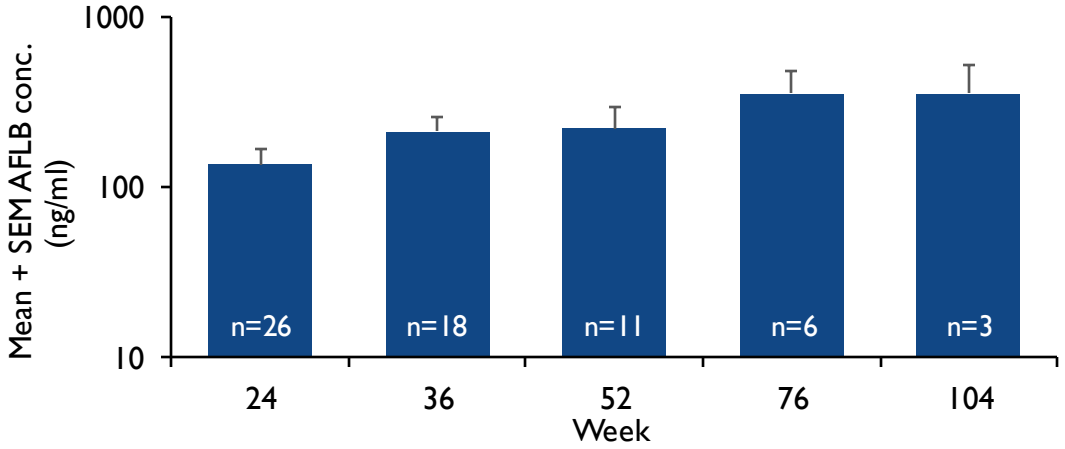
4D-150 Transgene Expression Stable for 2 Years

Durable and Stable Aflibercept Concentrations

Individual Participants



Mean AH Aflibercept Concentration

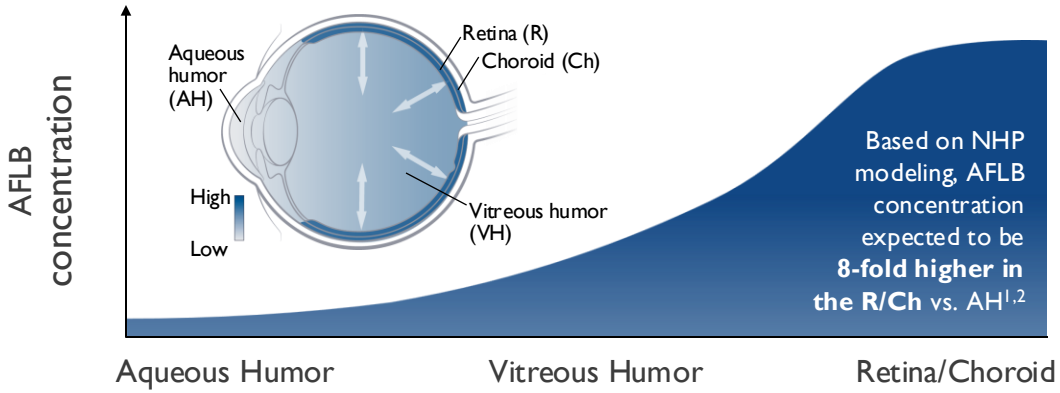


Analysis Population

Subjects with detectable AH aflibercept and no confounding supplemental injections within prior <20 weeks in the PRISM Phase 1/2a and Phase 2b 3×10^{10} vg/eye dose groups*

Key Findings

Robust and durable expression during follow up ranging from 9 months (Phase 2b) to up to 2 years (Phase 1/2a); Phase 2b levels consistent with the long-term trajectory in Phase 1/2a

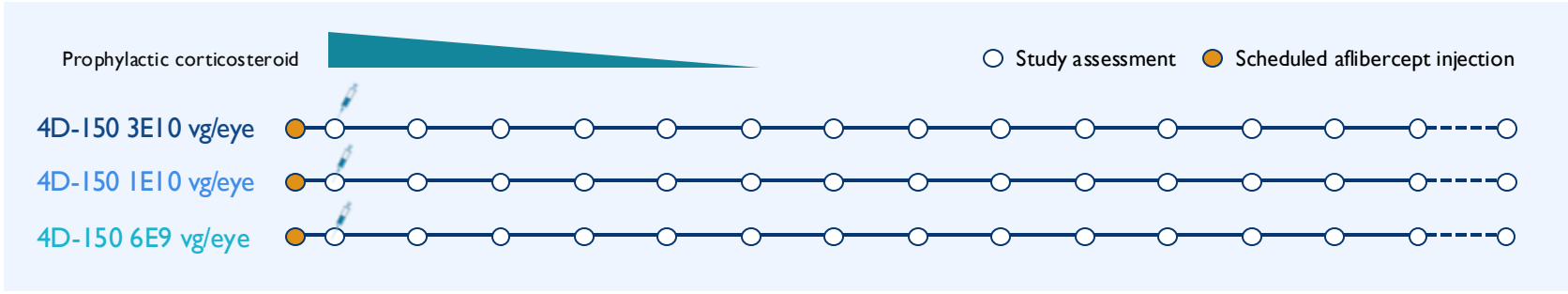


Preliminary data as of November 20, 2024. *Visits within 20 weeks after supplemental injections were excluded. Of 54 total subjects, 11 were non-evaluable at all visits due to supplemental injections. Of the 43 evaluable subjects, 29/43 (67%) had detectable AFLB levels at any visit; 14/43 (33%) were BLQ at any visit. Subjects were included in the line graph if they had at least two evaluable visits with levels above 30 ng/ml;. AFLB, aflibercept; AH, aqueous humor; BLQ, below the level of quantitation; NHP, nonhuman primate; R/Ch, retina/choroid; SEM, standard error of measurement. 1. Calton M. et al. *IOVS* 2024. 2. Khanani A et al. *ARVO* 2023.

4D-150 Wet AMD Clinical Development Program

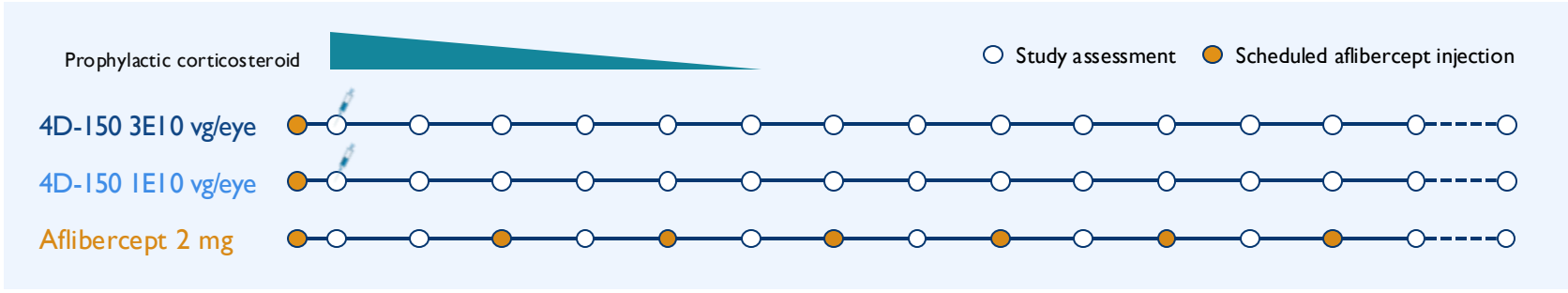
PRISM Phase 1/2 Clinical Trial

Phase 1
Dose Exploration



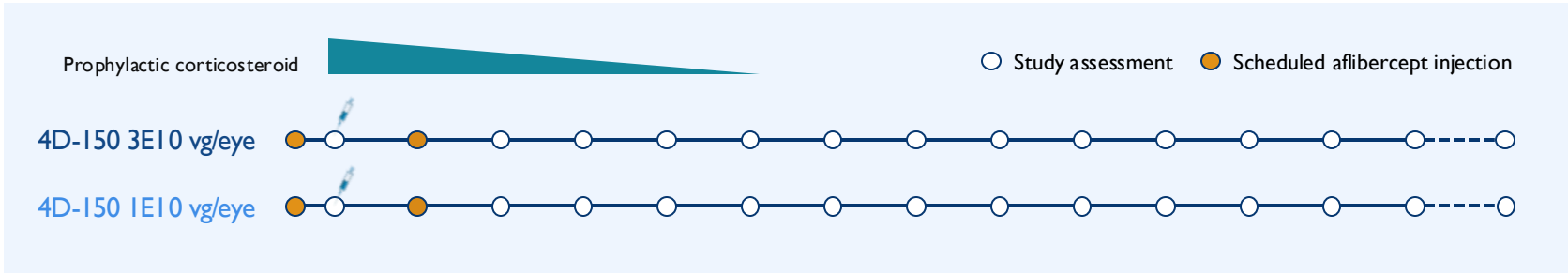
Population Characteristics*
BCVA: 65 letters
CST: 392 µm
Recently Diagnosed†: 0%
Time since Dx: 3.6 years

Phase 2a
Dose Expansion
(randomized 2:2:1)



Population Characteristics*
BCVA: 70 letters
CST: 442 µm
Recently Diagnosed†: 0%
Time since Dx: 3.1 years

Phase 2b
Population Extension



Population Characteristics*
BCVA: 72 letters
CST: 329 µm
Recently Diagnosed†: **50%**
Time since Dx: 1.4 years

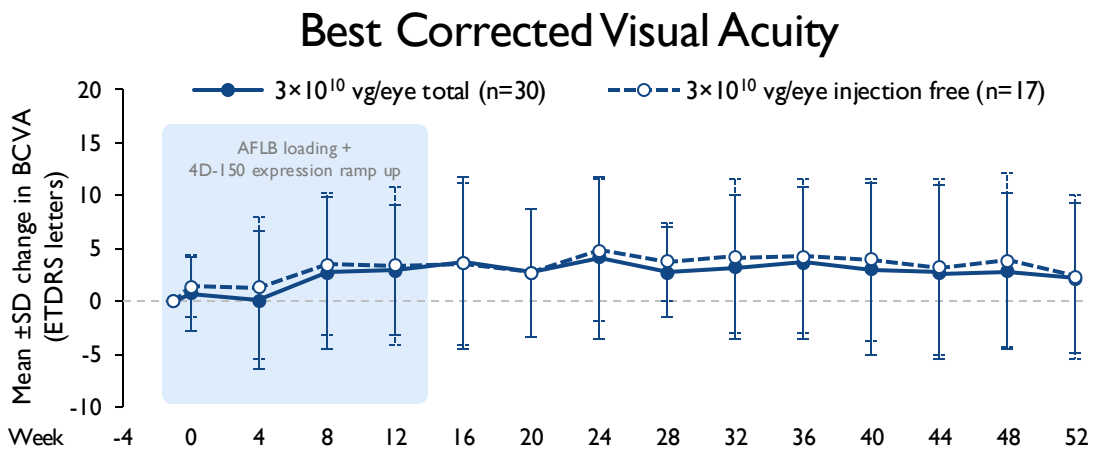
Week: –1 0 4 8 12 16 20 24 28 32 36 40 44 48 52 104

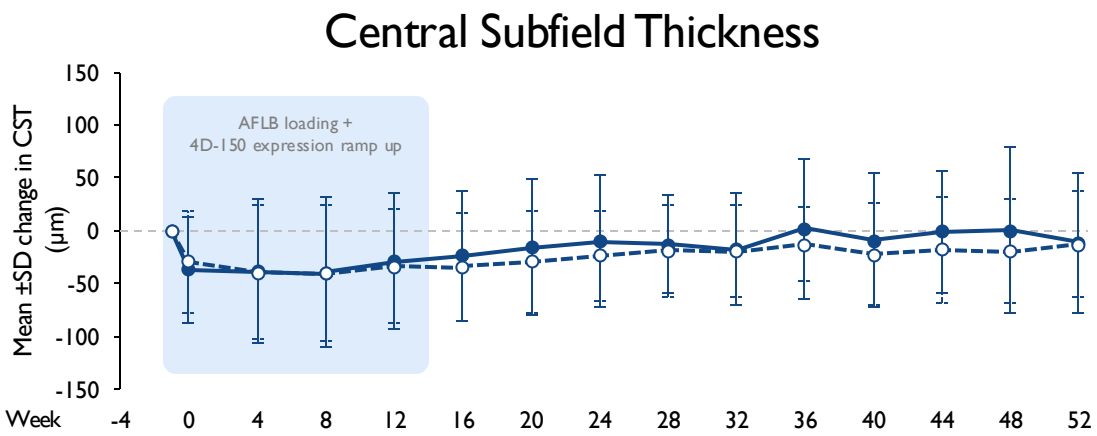
*Mean values unless otherwise indicated. †Defined as ≤0.5 years from baseline.

Best Corrected Visual Acuity & Central Subfield Thickness (Week 52)

Improved Visual Acuity and Sustained Anatomic Control

Visual Acuity and Anatomy



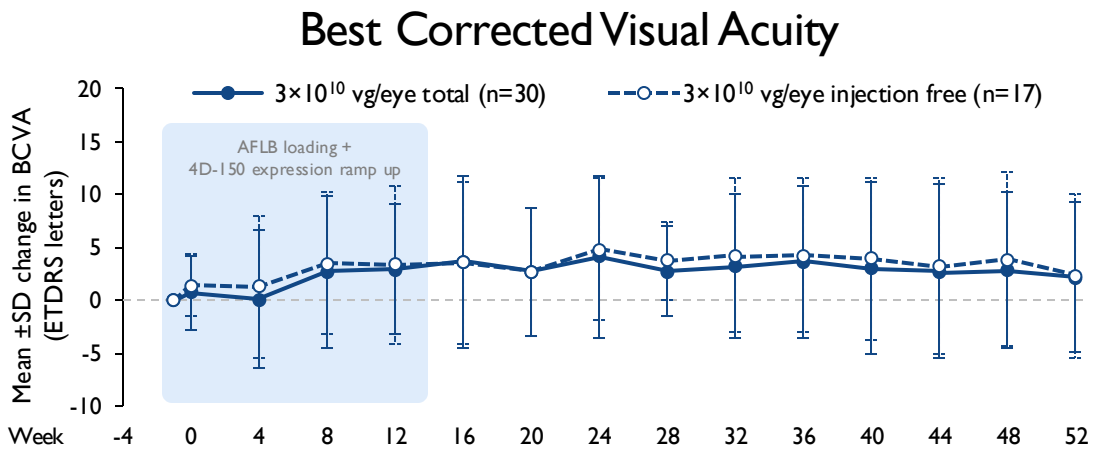


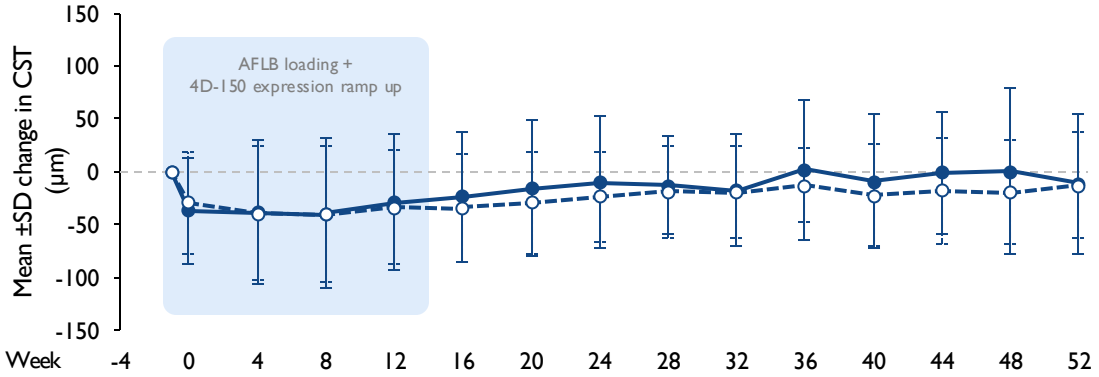
Best available data as of January 15, 2025. BCVA shown at each timepoint includes data for all participants except for missed visits (n=5 patients) or confounded assessments due to confounded by cataract or surgery (n=1 at 3 timepoints and n=1 at 7 timepoints); Week 52 mean change in BCVA without censoring, +1.0 letters.

Supplemental Anti-VEGF Injections Through Week 52 (Phase 2b)

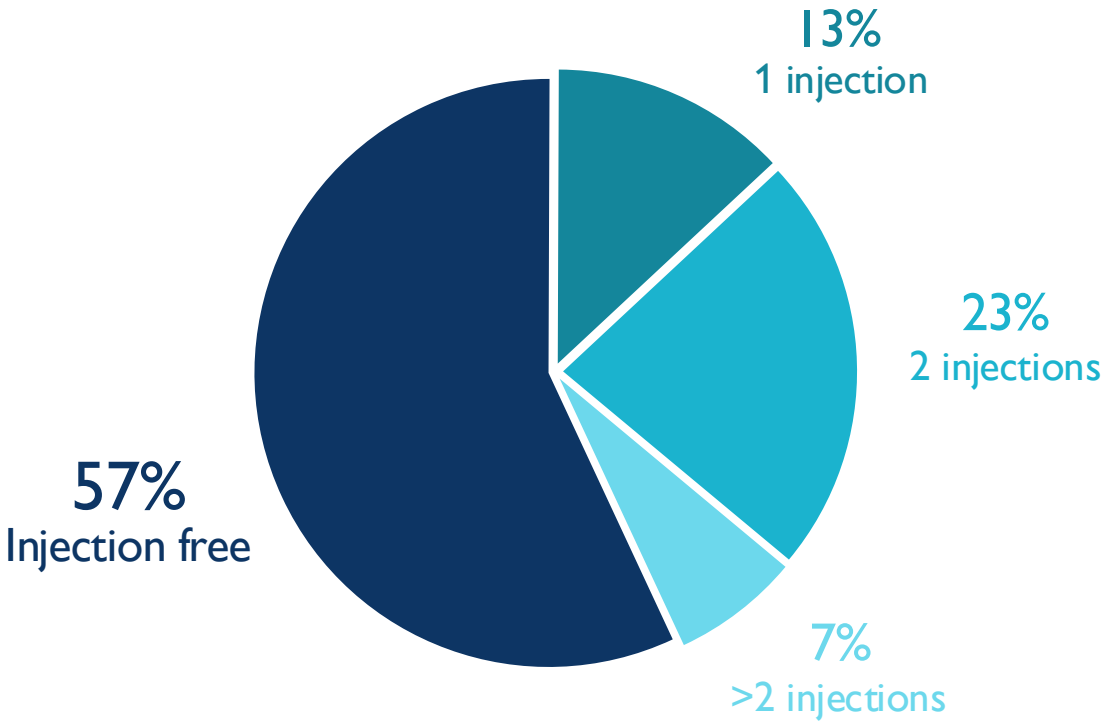
70% of Participants Received 0-1 Supplemental Injections

Visual Acuity and Anatomy





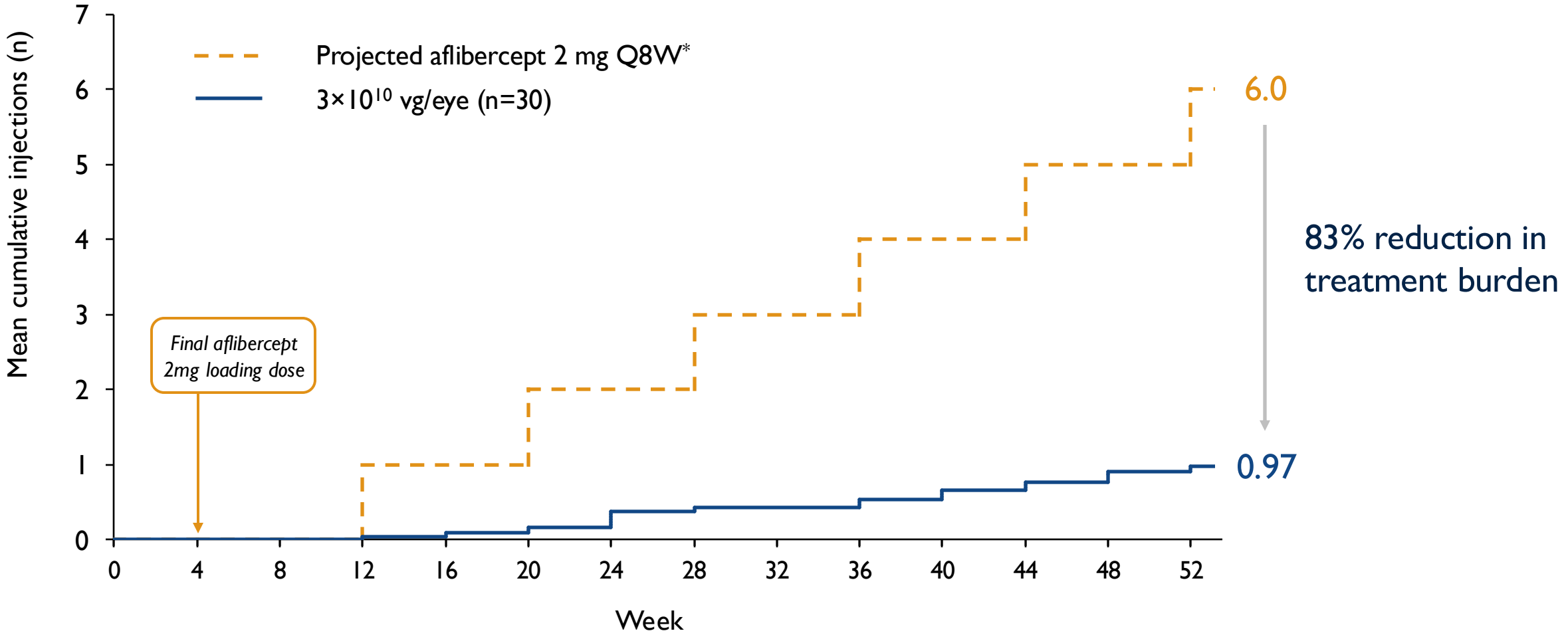
Supplemental Injections (Week 52)



Mean number of supplemental injections: **0.97**

Best available data as of January 15, 2025. BCVA shown at each timepoint includes data for all participants except for missed visits (n=5 patients) or confounded assessments due to confounded by cataract or surgery (n=1 at 3 timepoints and n=1 at 7 timepoints); Week 52 mean change in BCVA without censoring, +1.0 letters.

Mean Cumulative Number of Aflibercept Injections

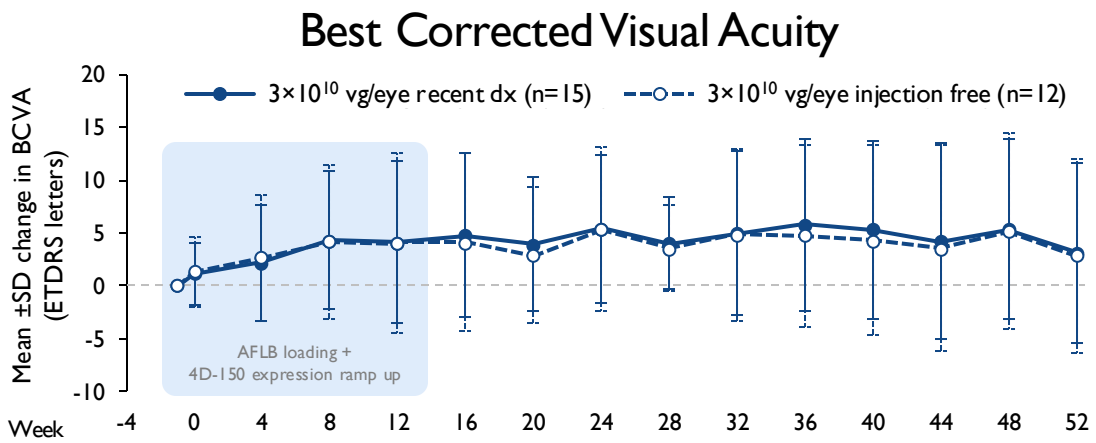


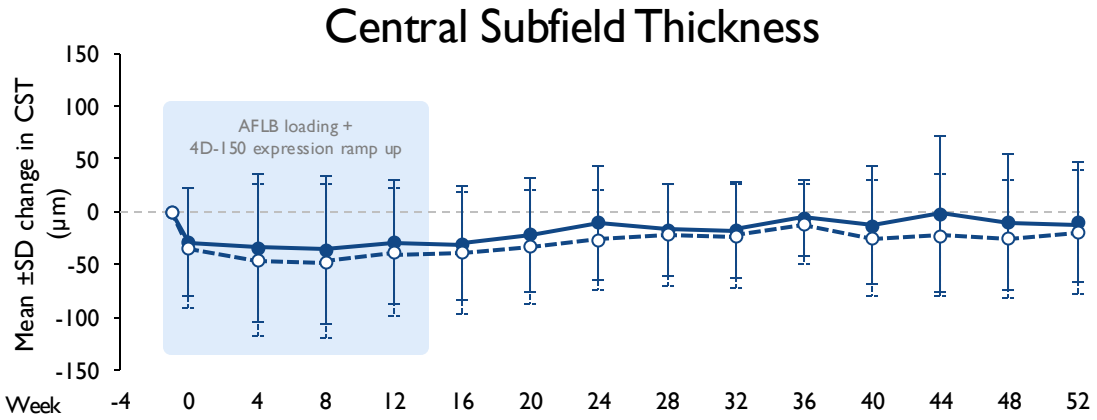
Mean cumulative function derived from a single-arm Cox proportional hazard regression model used to estimate the mean cumulative number of supplemental injections.
*Projection based on last loading dose in Phase 2b and approved dosing schedule for aflibercept in wet AMD.

Best Corrected Visual Acuity & Central Subfield Thickness (Recently Dx*)

Improved Visual Acuity and Sustained Anatomic Control

Visual Acuity and Anatomy





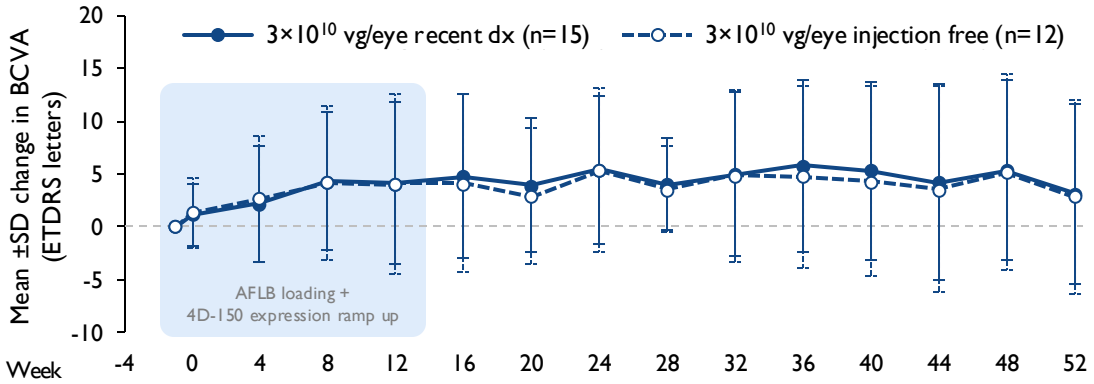
*Defined as ≤0.5 years from baseline.
Evaluable BCVA data shown at each timepoints in all patients except for missed visits (n=2 patients) or confounded assessments due to cataract or surgery (n=1 at 3 timepoints); Week 52 mean change in BCVA without censoring, +2.4 letters.

Supplemental Anti-VEGF Injections Through Week 52 (Recently Dx*)

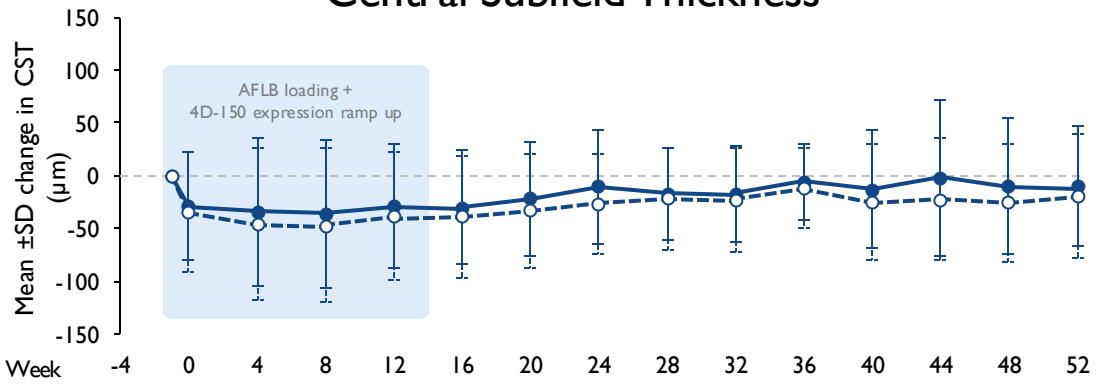
87% of Patients Received 0-1 Supplemental Injection

Visual Acuity and Anatomy

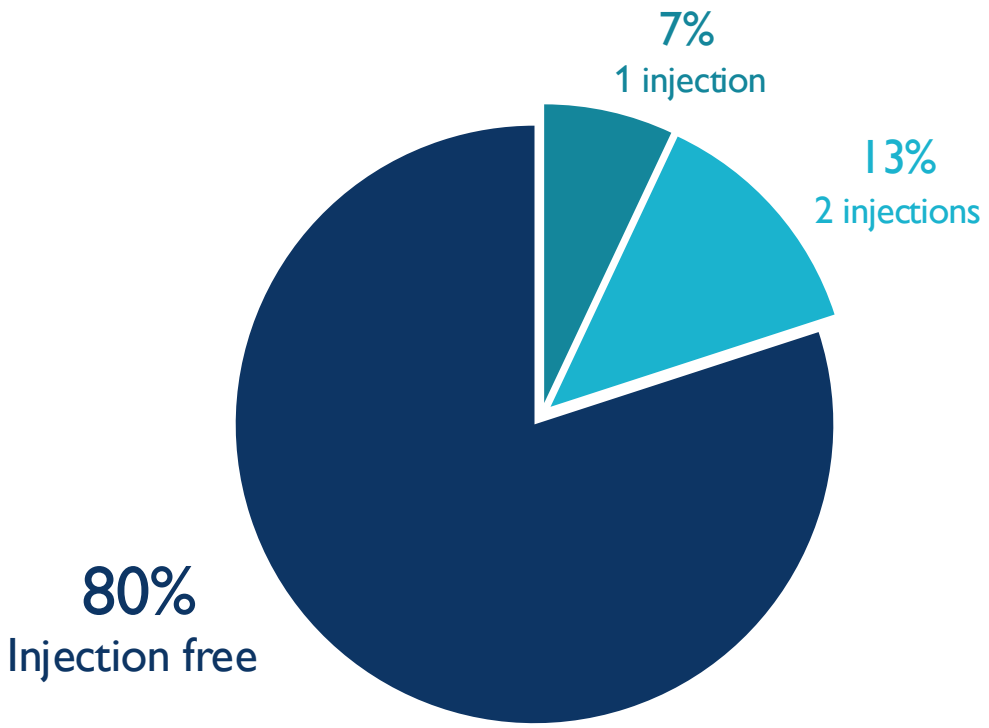
Best Corrected Visual Acuity



Central Subfield Thickness



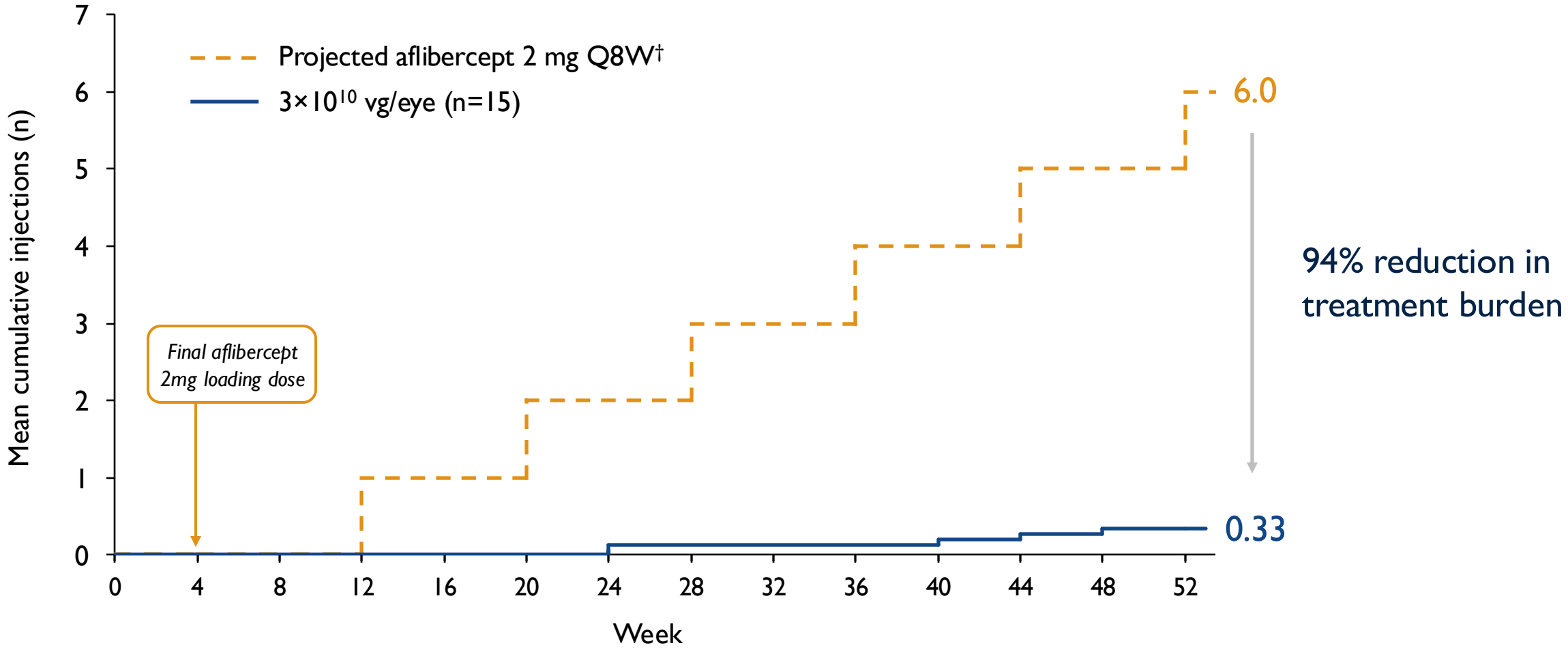
Supplemental Injections (Week 52)



Mean number of supplemental injections: **0.33**

*Defined as ≤0.5 years from baseline.
Evaluable BCVA data shown at each timepoints in all patients except for missed visits (n=2 patients) or confounded assessments due to cataract or surgery (n=1 at 3 timepoints); Week 52 mean change in BCVA without censoring, +2.4 letters.

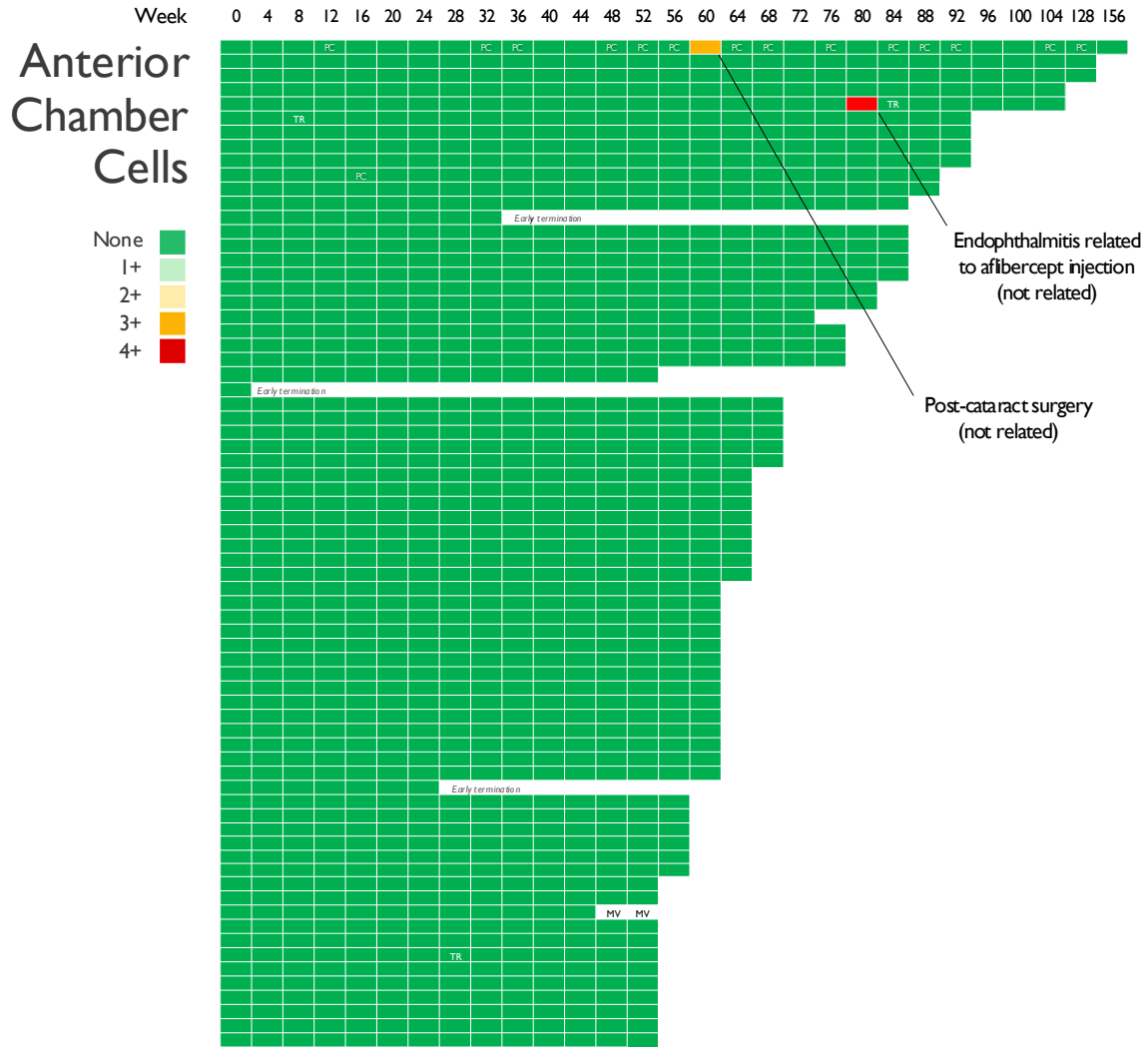
Mean Cumulative Number of Aflibercept Injections (Recently Dx*)

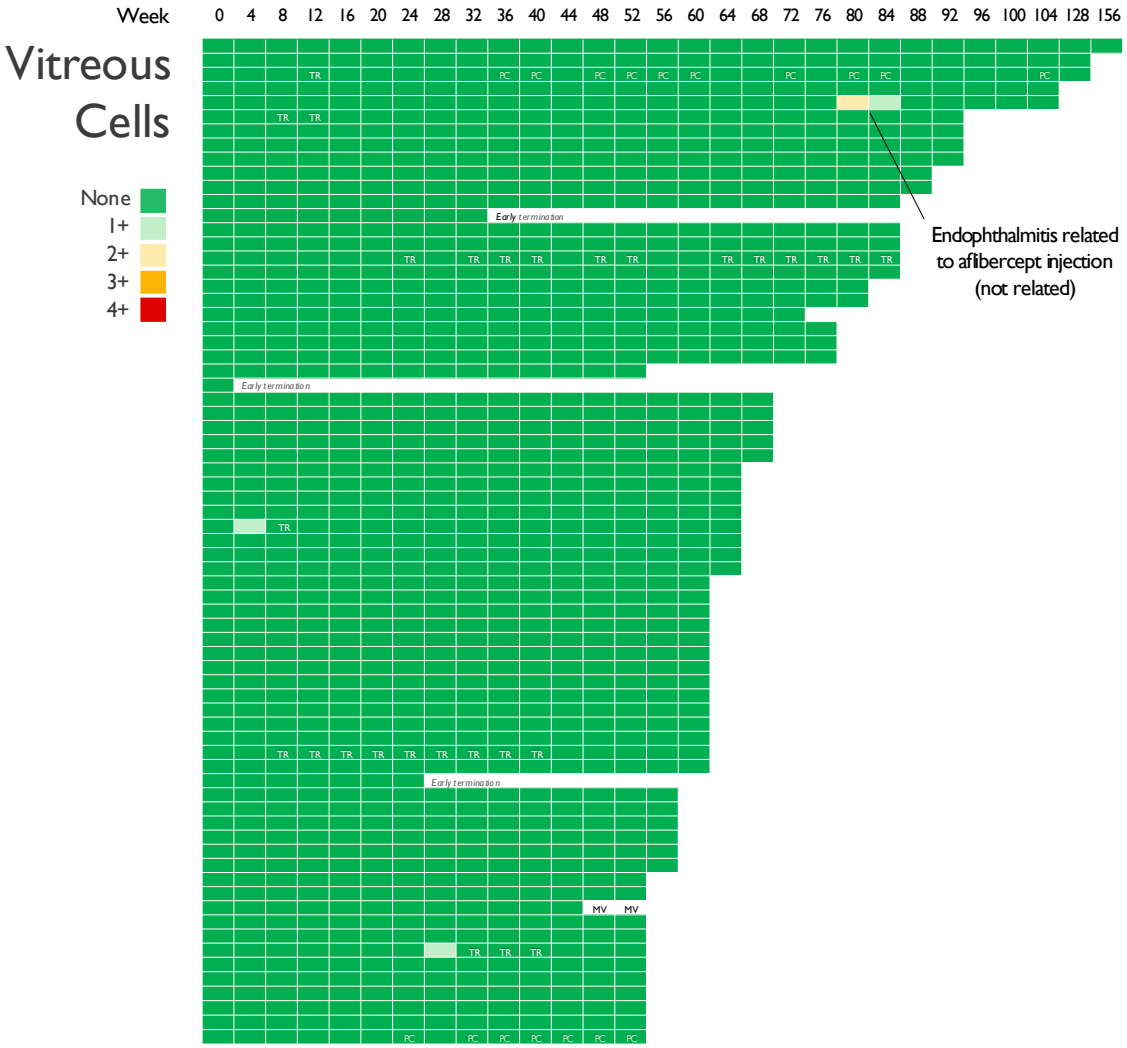


Mean cumulative function derived from a single-arm Cox proportional hazard regression model used to estimate the mean cumulative number of supplemental injections.
*Defined as ≤0.5 years from baseline. †Projection based on last loading dose and approved dosing schedule for aflibercept in wet AMD.

Ophthalmic Examination (3×10^{10} vg/eye)

4D-150 Remained Well Tolerated During up to 2.5 Years of Follow Up





SUN and NEI Scores for white blood cells. Missing visits with no inflammation observed at visits immediately before and after shown as none.
MV, missed visit; NEI, National Eye Institute; PC, pigmented cells; SUN, Standardization of Uveitis Nomenclature; TR, trace.

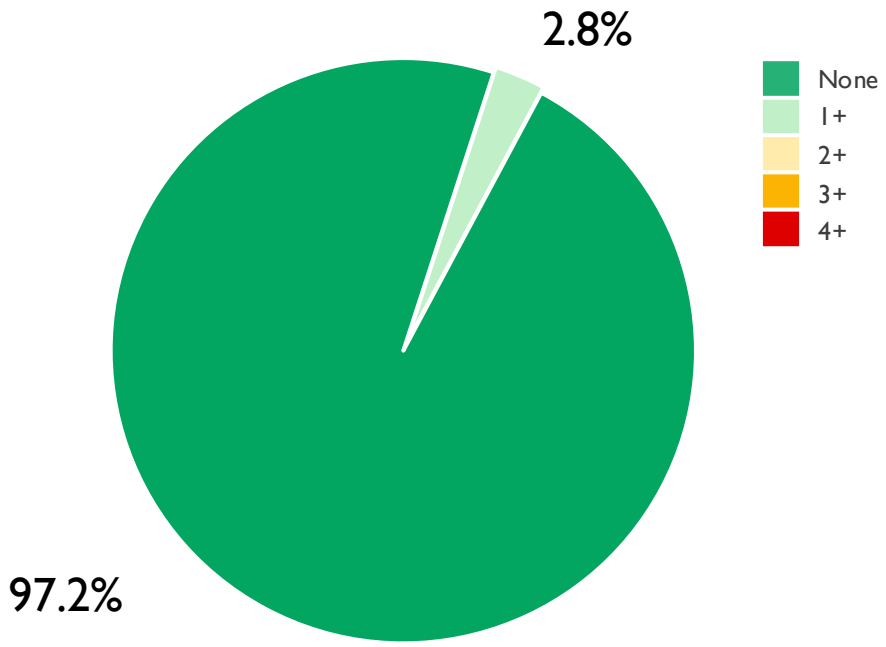
Safety and Tolerability

4D-150 Continues to be Well Tolerated Across PRISM 3×10^{10} vg/eye Cohorts*

- No 4D-150–related serious adverse events
- No 4D-150–related hypotony, endophthalmitis, occlusive/non-occlusive retinal vasculitis, or choroidal effusions
- Transient treatment-related IOI ≥1+ observed in 2 of 71 (2.8%) participants
- 99% (70 of 71) completed prophylactic steroid taper on schedule

4D-150 3×10^{10} vg/eye (N=71)*

Highest SUN/NEI Score†



*Duration of follow up, ≤3 years. †4D-150–related.
IOI, intraocular inflammation; NEI, National Eye Institute; SUN, Standardization of Uveitis Nomenclature; VC, vitreous cells.

Global 4FRONT Phase 3 wAMD Program

Primary Endpoint: Noninferiority of 4D-150 to Aflibercept 2mg Q8W in Change in BCVA at Week 52

Key Inclusion Criteria

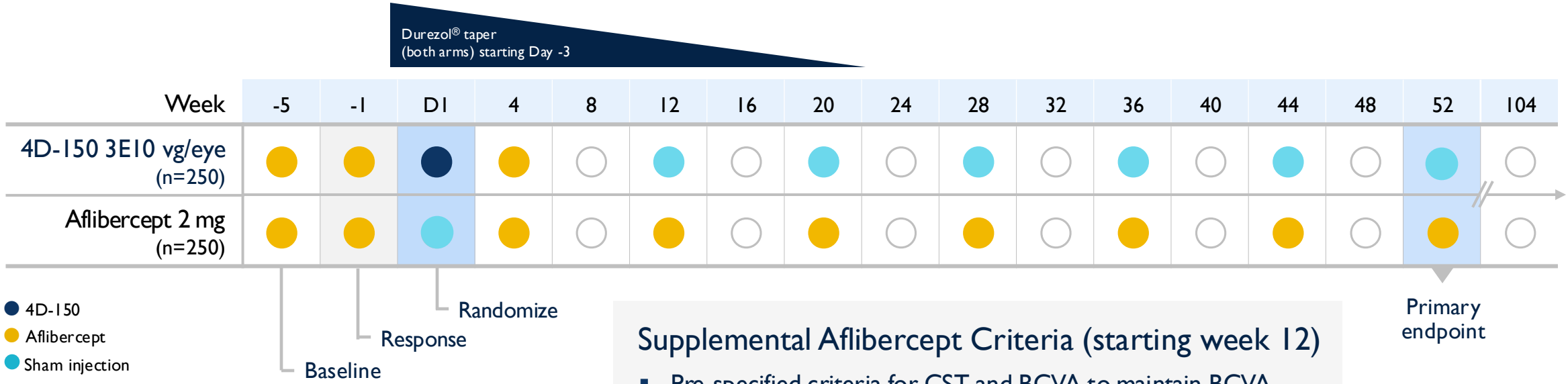
BCVA:
25-78 letters

Anti-VEGF responsive:
After Week -5 loading dose

Study Population

4FRONT-1
Treatment naïve

4FRONT-2
Treatment naïve & experienced
(diagnosed within 6 months)



Supplemental Aflibercept Criteria (starting week 12)

- Pre-specified criteria for CST and BCVA to maintain BCVA and protect primary endpoint
- Reference point: after 3 loading doses

PRISM Phase 2b Clinical Trial 52-week Results

Take Home Points

- Improved and maintained visual acuity
- Sustained anatomical control
- Robust reduction in anti-VEGF injection burden
  - Overall Phase 2b population (3×10^{10} vg/eye): ~83% reduction vs projected on-label aflibercept Q8W
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- Initiation of Phase 3 program anticipated in early 2025

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Allen Hu
Cumberland Valley Retina Consultants
Cumberland, MD

Christine Kay
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