Improved Anatomical Outcomes in ADVM-022 Treated Subjects Relative to Standard-of-Care Bolus Anti-VEGF Therapy: Results From the Phase 1 Study of Intravitreal (IVT) Gene Therapy With ADVM-022 for Neovascular AMD (OPTIC Trial)

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– On behalf of the OPTIC investigators –

Macula Society Annual Meeting • June 8-11, 2022

Disclosures

- Adverum Biotechnologies – Consultant/Advisor, Equity
- Regenxbio – Consultant/Advisor, Equity
- Genentech/Roche – Consultant/Advisor
- Fortress Bio – Consultant/Advisor, Equity
- Optos – Consultant/Advisor, Research grant support
- Novartis – Consultant/Advisor
- Intellectual Property related to gene and cellular therapy – assigned to Weill Cornell/Cornell University

OPTIC Study: Designed to Evaluate the Efficacy and Safety of ADVM-022 for nAMD

Status

- 4 cohorts fully enrolled
- Follow-up to 104 weeks

Primary Objective

- Assess the safety and tolerability of a single IVT injection of ADVM-022

Secondary Objective

- Evaluate vision maintenance (BCVA)
- Evaluate anatomy (SD-OCT)
- Assess the need for supplemental therapy

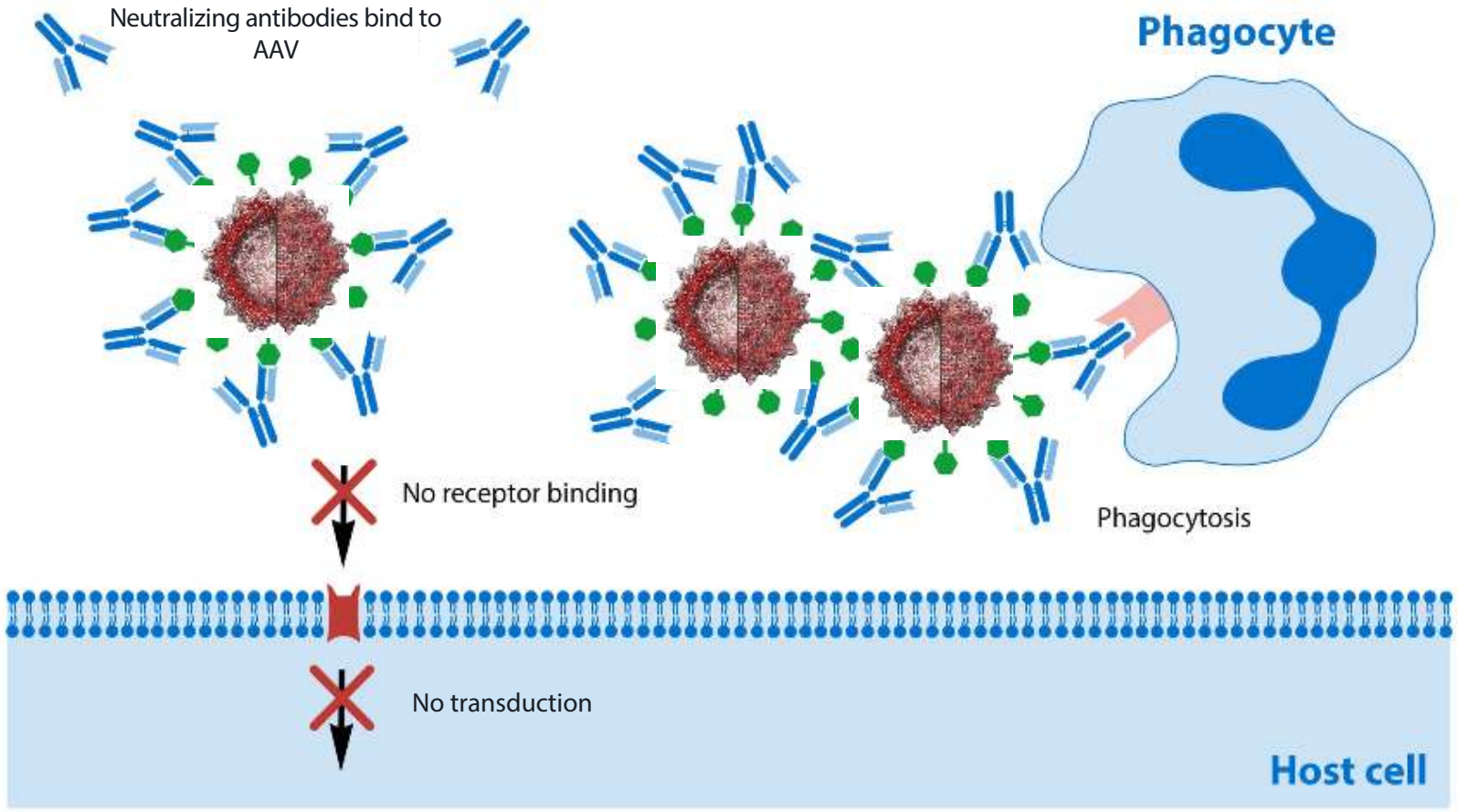
	Prophylactic Steroid Regimen
Cohort 1 (n=6) 6 x 10^{11} high dose	Oral*, 13d
Cohort 2 (n=6) 2 x 10^{11} low dose	Oral*, 13d
Cohort 3 (n=9) 2 x 10^{11} low dose	Eye Drops**, 6wks
Cohort 4 (n=9) 6 x 10^{11} high dose	Eye Drops**, 6wks

Neutralizing Antibodies (NAbs) to AAV.7m8

- An assay was used to detect anti-AAV antibodies with the capacity to neutralize AAV.7m8 in human serum
- NAbs exclusion criteria were a titer level of >1:5 for cohort 1 and >1:125 for cohorts 2-4
- The impact of baseline NAbs on treatment burden, aflibercept protein expression levels, CST fluctuations, and safety outcomes was evaluated

**Subjects received prophylaxis of 60 mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper. **Subjects received prophylaxis of QID difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper. AAV, adeno-associated virus; AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CST, central subfield thickness; IVT, intravitreal therapy; NAb, neutralizing antibody; QID, four times daily; SD-OCT, spectral domain optical coherence tomography; NCT03748784.*

Neutralizing Antibodies May Reduce AAV-driven Gene Therapy Transduction



The presence of NAbs can lead to a reduction in transduction efficiency[1,2]

AAV, adeno-associated virus; NAb, neutralizing antibody.

1. Verdera HC, et al. Mol Ther. 2020;28(3):723-746; 2. Fitzpatrick Z, et al. Mol Ther Methods Clin Dev. 2018;9:119-129.

Low Prevalence of NAbs Against Engineered AAV.7m8

Prevalence of Naturally Occurring NAbs to AAV: Literature

The definition of what neutralizing titer qualifies an individual as being considered seropositive varies between studies, although most studies used a cutoff of 1/20 (Table 1)

TABLE 1. PREVALENCE OF NEUTRALIZING ANTIBODIES AGAINST AAV SEROTYPES

Study	*Dilution*	*AAV1*	*AAV2*	*AAV5*	*AAV6*	*AAV7*	*AAV8*	*AAV9*
Boutin *et al.*, 2010	1/20	50	59	3	37		19	33
Chirmule *et al.*, 1999	1/20 (?)		32					
Murphy *et al.*, 2009	1/3.1		38					
Calcedo *et al.*, 2009; Australia	1/20	30	35			29	27	
Calcedo *et al.*, 2009; Europe	1/20	27	35			25	22	
Calcedo *et al.*, 2009; Africa	1/20	43	56			31	31	
Calcedo *et al.*, 2009; United States*	1/20	20	28			12	14	
Halbert *et al.*, 2006*			30	18	30	14	30	
Parks *et al.*, 1970	1/10		40					
Blacklow *et al.*, 1968	1/10		40					
Ito *et al.*, 2009	1/20		40					
Moss *et al.*, 2004	?		32					
Wagner *et al.*, 2002	1/20		22					
Erles *et al.*, 1999*			50	50				
Veron *et al.*, 2012	1/2	59						
Mingozzi *et al.*, 2012a	1/10		82	27	64		50	
	1/3.1		100	36	91		90	

The numbers in the columns of specific AAV serotypes indicate the percentage of subjects whose serum inhibited transduction by ≥50% at the indicated serum dilution.
*Approximate values.

Average prevalence to AAV2 across studies ~40%

Prevalence of NAbs titer >1:125 to AAV.7m8

Estimate: ~20% Based on cross-reactivity of A20 and C37-B NAbs to AAV.7m8

Actual in OPTIC: ~20%

Screening:
13% of 60 participants

Enrolled:
20% of 30 participants

AAV.7m8 is an engineered vector with naturally occurring NAbs predicted to be lower than native AAV2

Louis Jeune, V., Joergensen, J. A., Hajjar, R. J., & Weber, T. (2013). Pre-existing anti–adeno-associated virus antibodies as a challenge in AAV gene therapy. Human Gene Therapy Methods, 24(2), 59–67. https://doi.org/10.1089/hgtb.2012.243

Baseline Characteristics and Participant Status

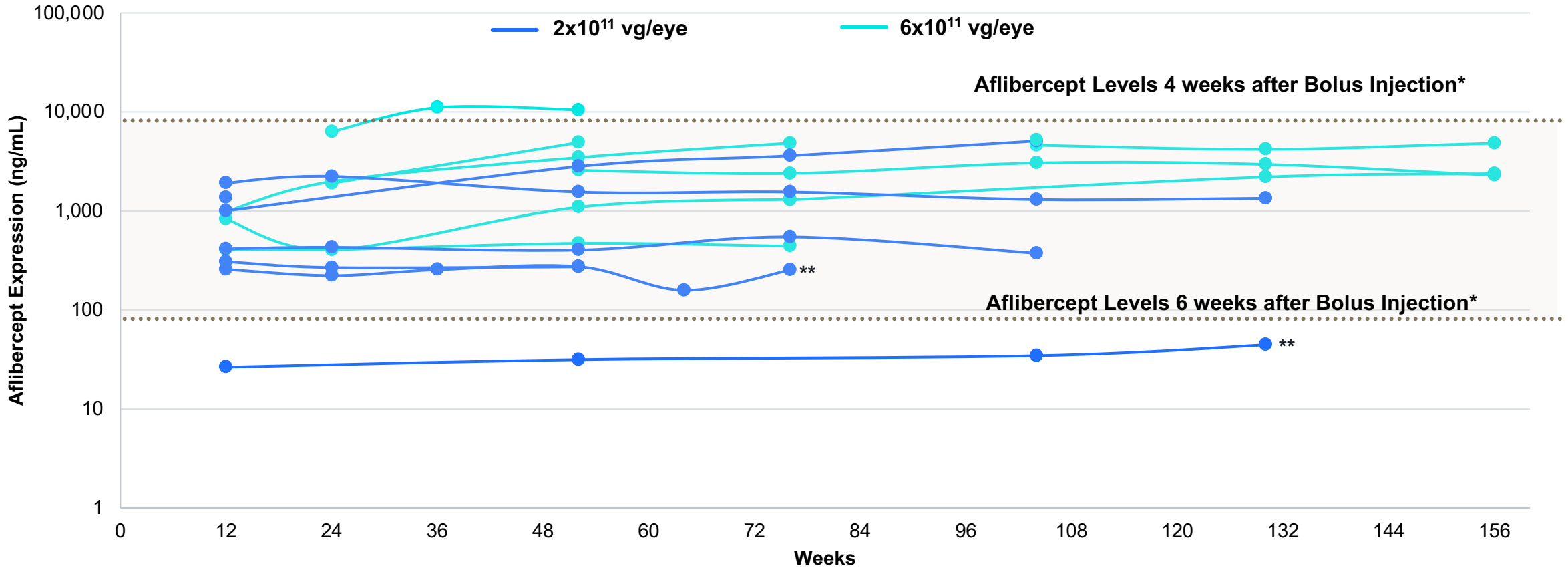
Baseline Characteristics	Cohort 1 $6x10^{11}$ (N=6)	Cohort 2 $2x10^{11}$ (N=6)	Cohort 3 $2x10^{11}$ (N=9)	Cohort 4 $6x10^{11}$ (N=9)
Mean (range) Age, Years	79.0 (62–88)	79.8 (74–90)	77.4 (65–90)	79.9 (68–88)
Mean (range) Years Since nAMD Diagnosis	4.5 (0.9–10.6)	4.1 (0.5–6.8)	3.3 (0.7–8.0)	3.2 (0.2–8.0)
Mean (range) Number anti-VEGF Injections Since Initial Diagnosis*	38.2 (7–109)	34.0 (4–69)	24.8 (9–70)	28.5 (2–58)**
Mean (range) Number anti-VEGF Injections in 12 Months Prior to ADVM-022	9.2 (8–11)	9.2 (6–11)	8.9 (7–10)	6.6 (3–12)**
Mean (range) BCVA, ETDRS Letters Approximate Snellen Equivalent	65.8 (57–77) 20/50	64.7 (53–72) 20/50	65.9 (53–75) 20/50	65.0 (54–77) 20/50
Mean (range) CST, µm	369.2 (293–561)	307.7 (235–339)	473.4 (301–857)	398.6 (255–538)
NAbs <1:125, n (%)	6 (100%)	4 (67%)	6 (67%)	8 (89%)
Participant Status				
Follow-Up	2 years (Completed)	2 years (Completed)	2 years (Completed)	60–92 weeks (median 84)

**Not including the mandated aflibercept at Screening; **Excluding participant #2 with incomplete prior anti-VEGF data;*
BCVA, best corrected visual acuity: CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; NAbs, neutralizing antibodies; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor

Data Cut: Feb 24, 2022

ADVM-022: Continuous Therapeutic Aflibercept Expression Levels Sustained Out to 3 Years

Individual Participant Plots



*Modeled based on Do et al. Retina 2020; 40:643-647.

** Participant received supplemental aflibercept injections

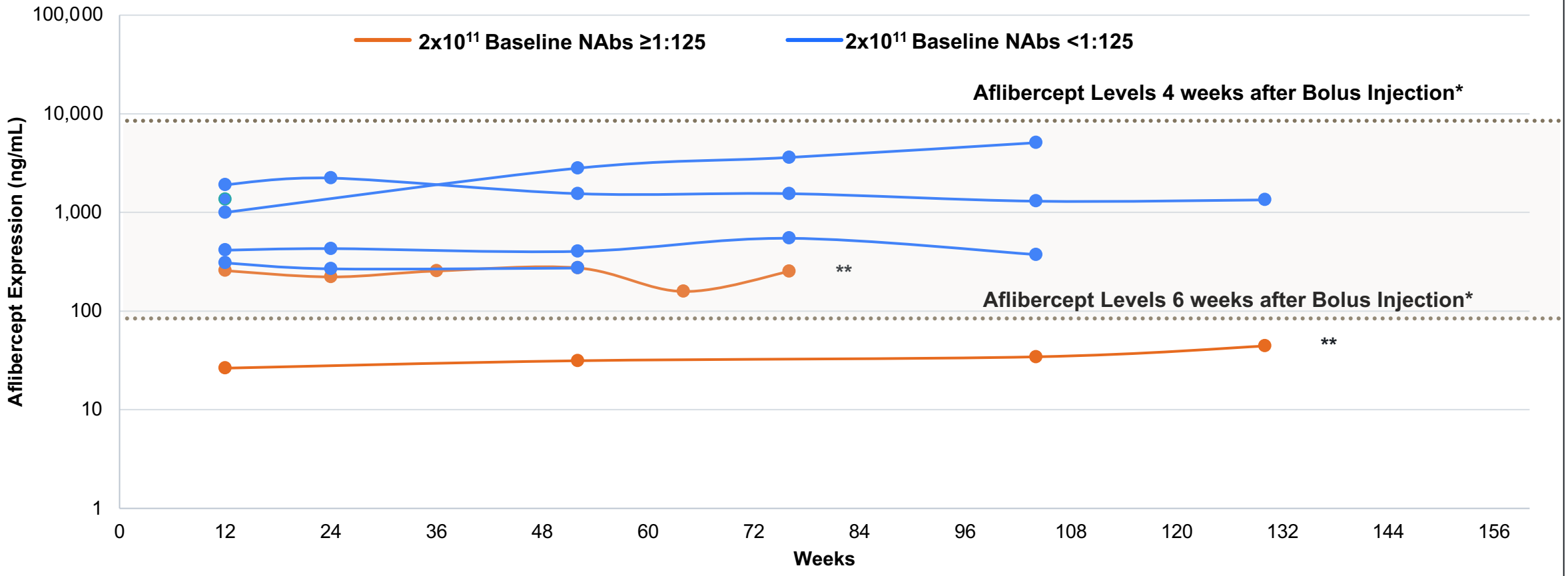
Protocol amendment for aqueous sample collection for participants that consented.

To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.

Data Cut: Feb 24, 2022

All Participants With NAbs <1:125 Demonstrated Sustained Therapeutic Levels of Aflibercept

Individual Participant Plots



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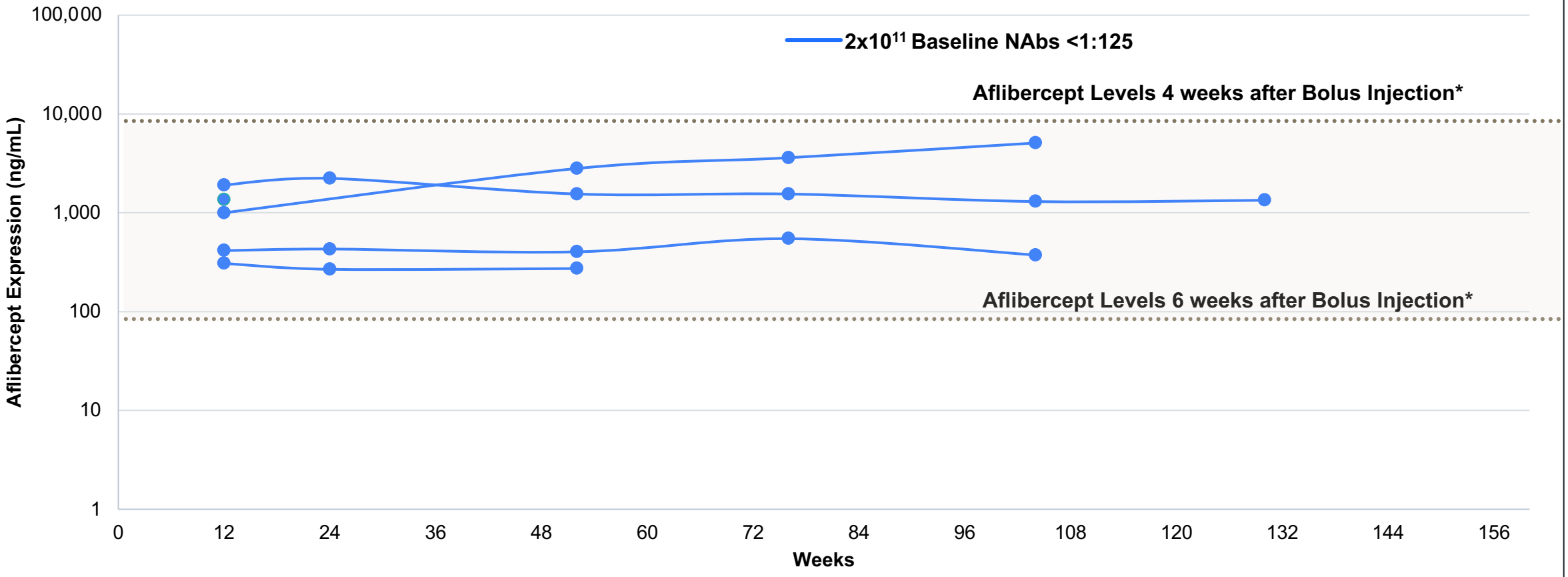

*Modeled based on Do et al. Retina 2020; 40:643-647.

Protocol amendment for aqueous sample collection for participants that consented.

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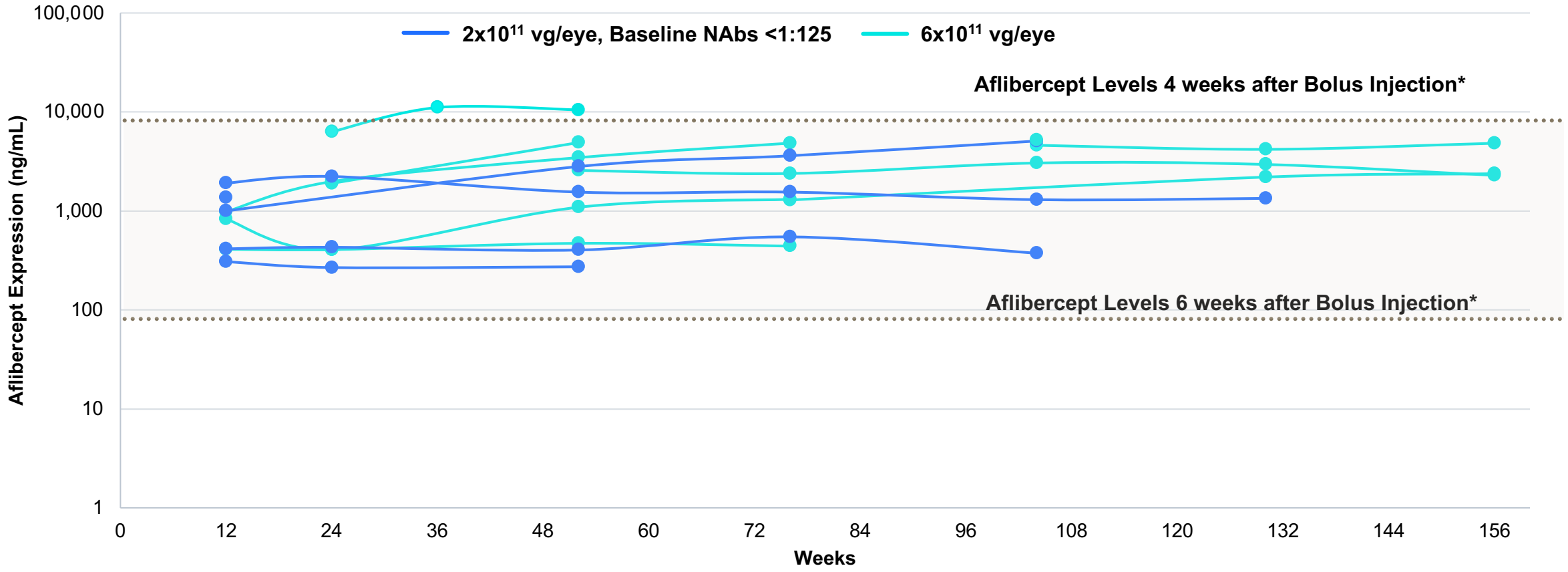
ADVM-022: Low Dose ($2x10^{11}$) With NAbs <1:125 Provides Comparable Sustained Therapeutic Aflibercept Expression to High Dose ($6x10^{11}$)

Individual Participant Plots



*Modeled based on Do et al. Retina 2020; 40:643-647.

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To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.

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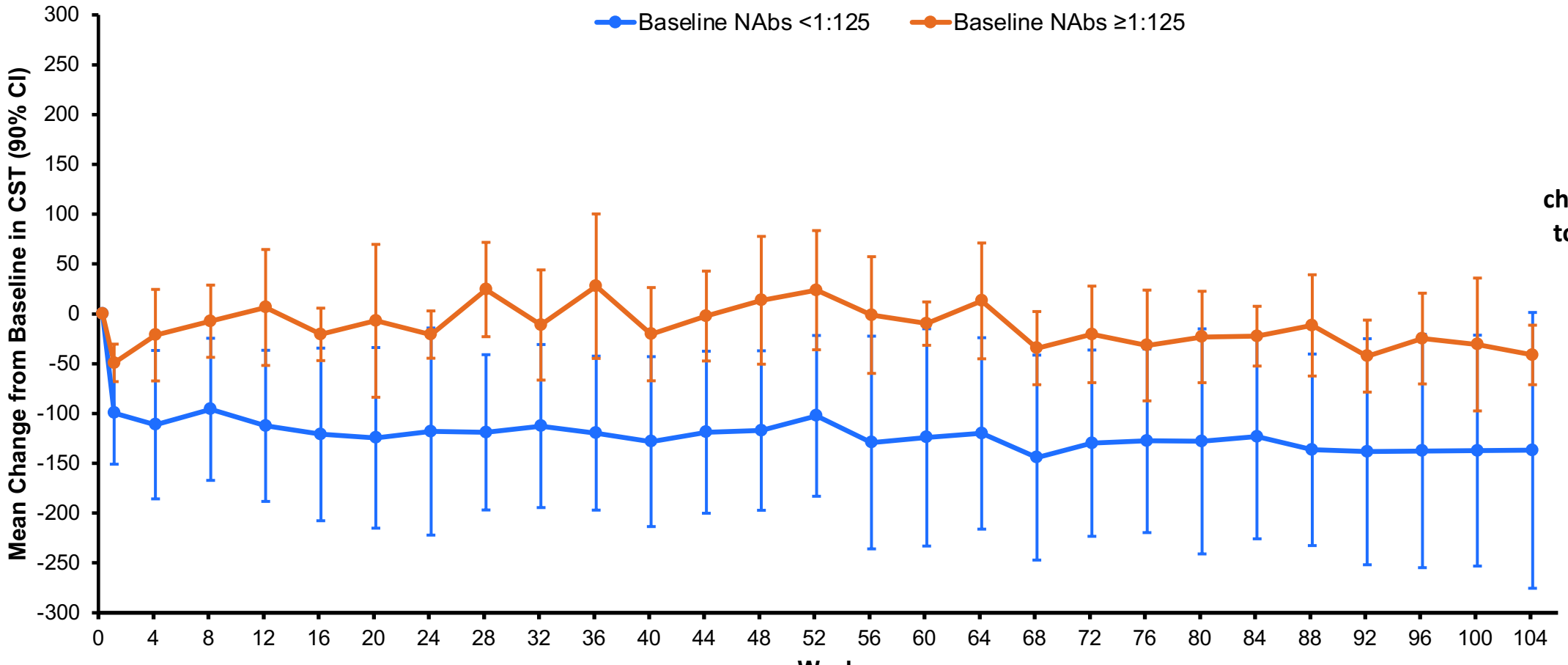
Mean CST Significantly Reduced in Both NAbs Subgroups

Mean Change from Baseline in CST (90% CI) by NAbs Group, $2x10^{11}$ Dose



	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104
Baseline NAbs <1:125	10	9	10	10	9	9	8	10	10	10	9	10	10	8	8	8	9	8	9	9	8	9	9	8	8	8	7
Baseline NAbs ≥1:125	5	5	5	5	5	5	5	5	5	4	5	5	5	4	5	5	5	5	5	4	5	5	5	5	5	4	4

Mean CST (µm) change from baseline to last visit (90% CI)

Baseline NAbs ≥1:125: -34.4 (-59.9, -8.9) p=0.045*

Baseline NAbs <1:125: -126.6 (-216.7, -36.5) p=0.030*

**Derived from a paired t-test comparing mean CST pre-ADVM-022 and at the last visit post-ADVM-022*

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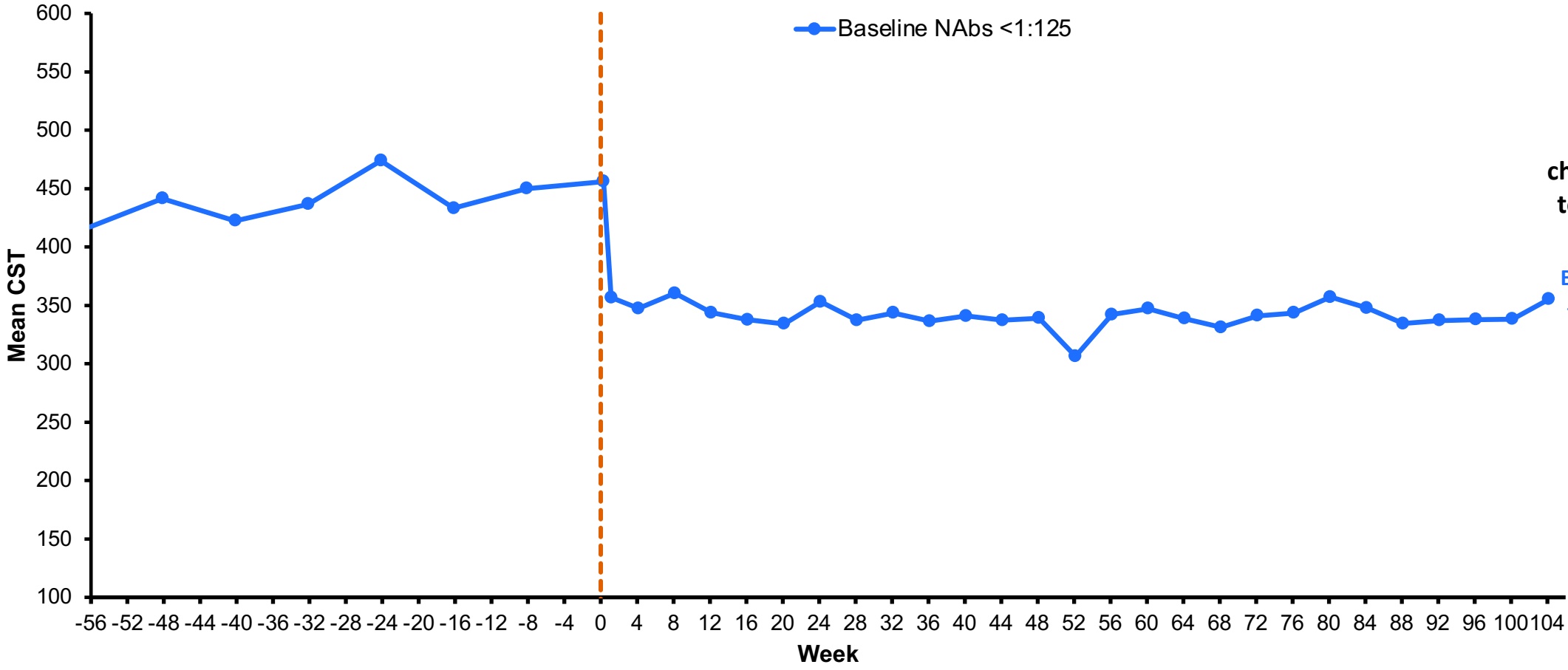
In 2x10[11] Participants With NAbs <1:125, Significant Improvement in CST Observed vs Year Prior in a Difficult to Treat Population

Mean CST with Historical Data by Cohort And Week



Mean CST (µm) change from baseline to last visit (90% CI)

Baseline NAbs <1:125: -126.6 (-216.7, -36.5) p=0.030*

Baseline NAbs <1:125	3		7		7		8		9		9		9		10	9	10	10	9	9	8	10	10	10	9	10	10	8	8	8	9	8	9	9	8	9	9	8	8	8	7

**Derived from a paired t-test comparing mean CST pre-ADVM-022 and at the last visit post-ADVM-022*

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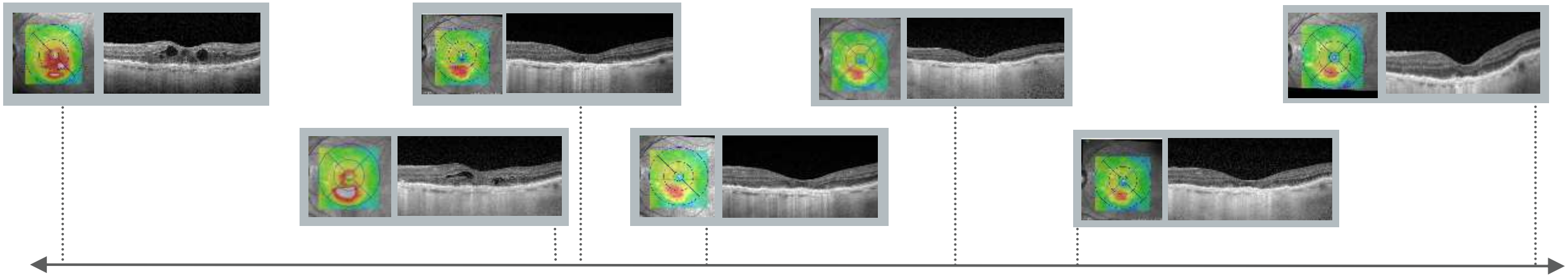
Case Study: 90-year-old Female With 21 IVTs Prior to Study and No Supplemental Anti-VEGF Injections Out to 100 Weeks

Cohort 3 ($2x10^{11}$ vg/eye) Participant with Baseline NAbs <1:125



-56 wks

-2 wks
BCVA: 53 letters
CST: 358µm

Day 0
ADVM-022

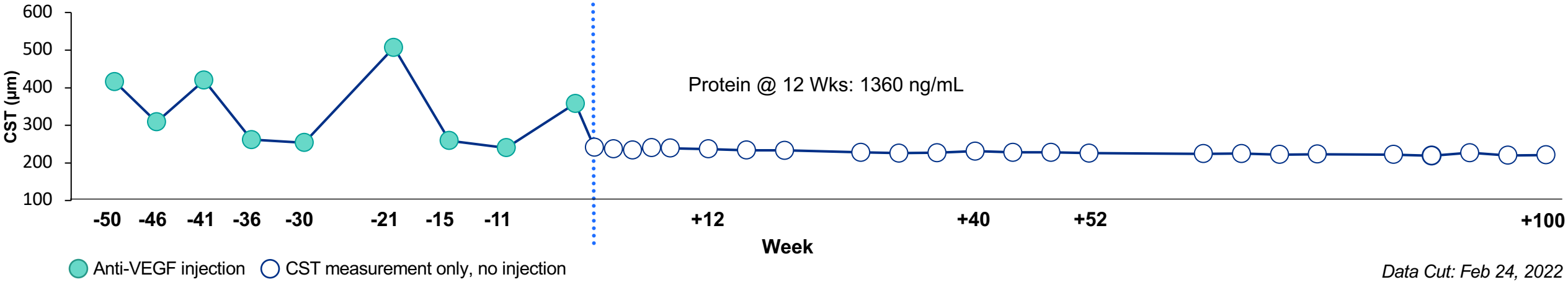
+12 wks
BCVA: 66 letters
CST: 237µm

+40 wks
BCVA: 71 letters
CST: 231 µm

+52 wks
BCVA: 69 letters
CST: 226 µm

+100 wks
BCVA: 66 letters
CST: 221 µm

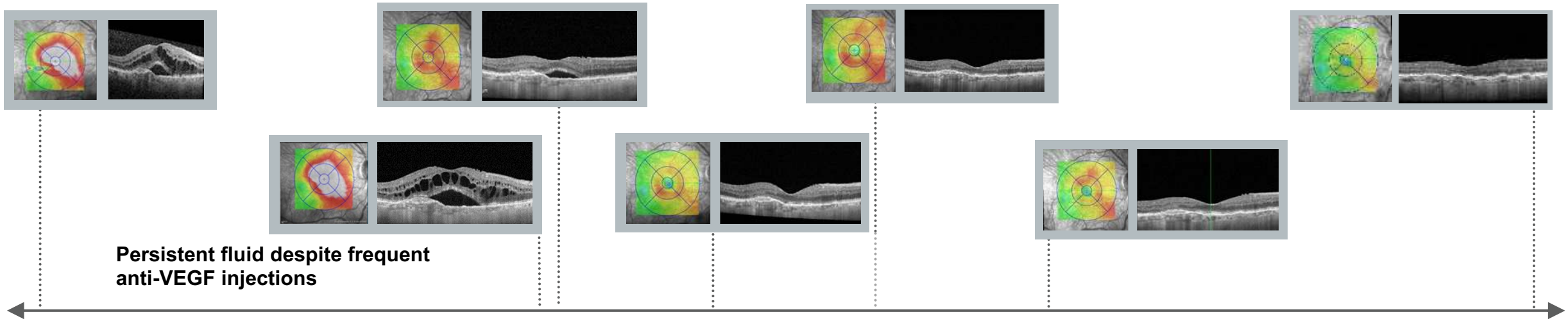
Treatment with aflibercept Q5W



Data Cut: Feb 24, 2022

Case Study: 82-year-old Male With 19 IVTs Prior to Study and No Supplemental Anti-VEGF Injections Out to 104 Weeks

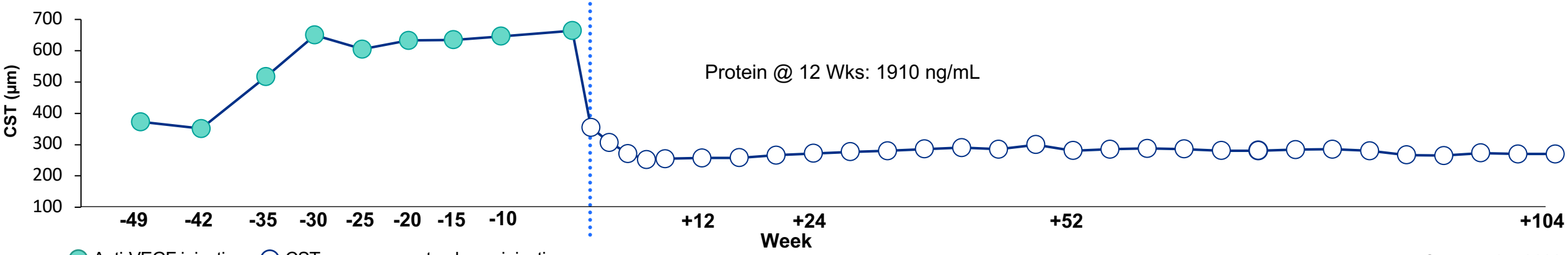
Cohort 3 ($2x10^{11}$ vg/eye) Participant with Baseline NAbs <1:125



Persistent fluid despite frequent anti-VEGF injections

-30 wks	-2 wks	Day 0 ADVM-022	+12 wks	+24 wks	+52 wks	+104 wks
	BCVA: 75 letters CST: 664 µm		BCVA: 81 letters CST: 257 µm	BCVA: 83 letters CST: 272 µm	BCVA: 83 letters CST: 281 µm	BCVA: 84 letters CST: 270 µm

Treatment with aflibercept Q5W



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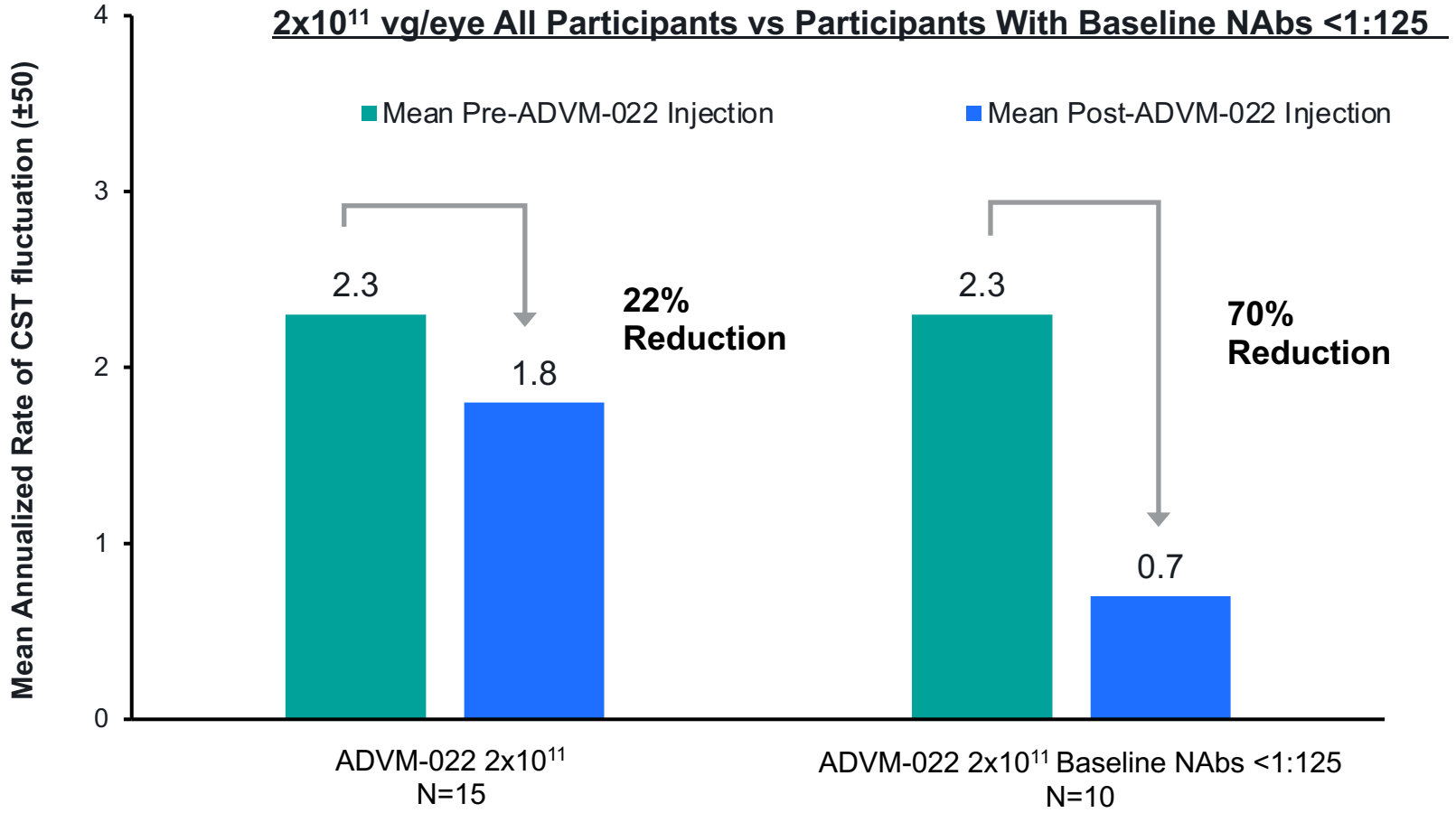
70% Reduction in Annualized Rate of CST Fluctuation (± 50 microns) Observed Among Participants With NAbs <1:125 Treated With ADVM-022 2x10^{11} vg/eye



Central retinal thickness fluctuations have been associated with poorer visual outcomes[1-4]

Annualized Rate of Fluctuations Pre-ADVM-022 = (number of fluctuations since first historical observation)/(days from first historical observation to the last historical observation/365.25).
Annualized Rate of Fluctuations Post-ADVM-022 = (number of fluctuations since ADVM-022 injection)/(days from ADVM-022 to the last study follow-up/365.25).
Starting from the first historical observation (pre-ADVM-022 injection) or from Day 1 (date of ADVM-022 injection), a fluctuation is defined as a change over a given week interval with a magnitude of at least ± 50, and where the direction of change (positive or negative) remains the same for any interim weeks in the interval and where the opposite direction of change is observed in the week immediately following the given week interval.

1. Evans, et al. JAMA Ophthalmol. 2020;138(10):1043-1051. 2. Chen, et al. Can J Ophthalmol. 2021 Jul 17:S0008-4182(21)00211-8.
3. Ciucci, et al. EUR J Ophthalmol 2021 Aug 14;11206721211037820.2021. 4. Chakravarthy, et al. Eye (2021) 35:2983–2990.

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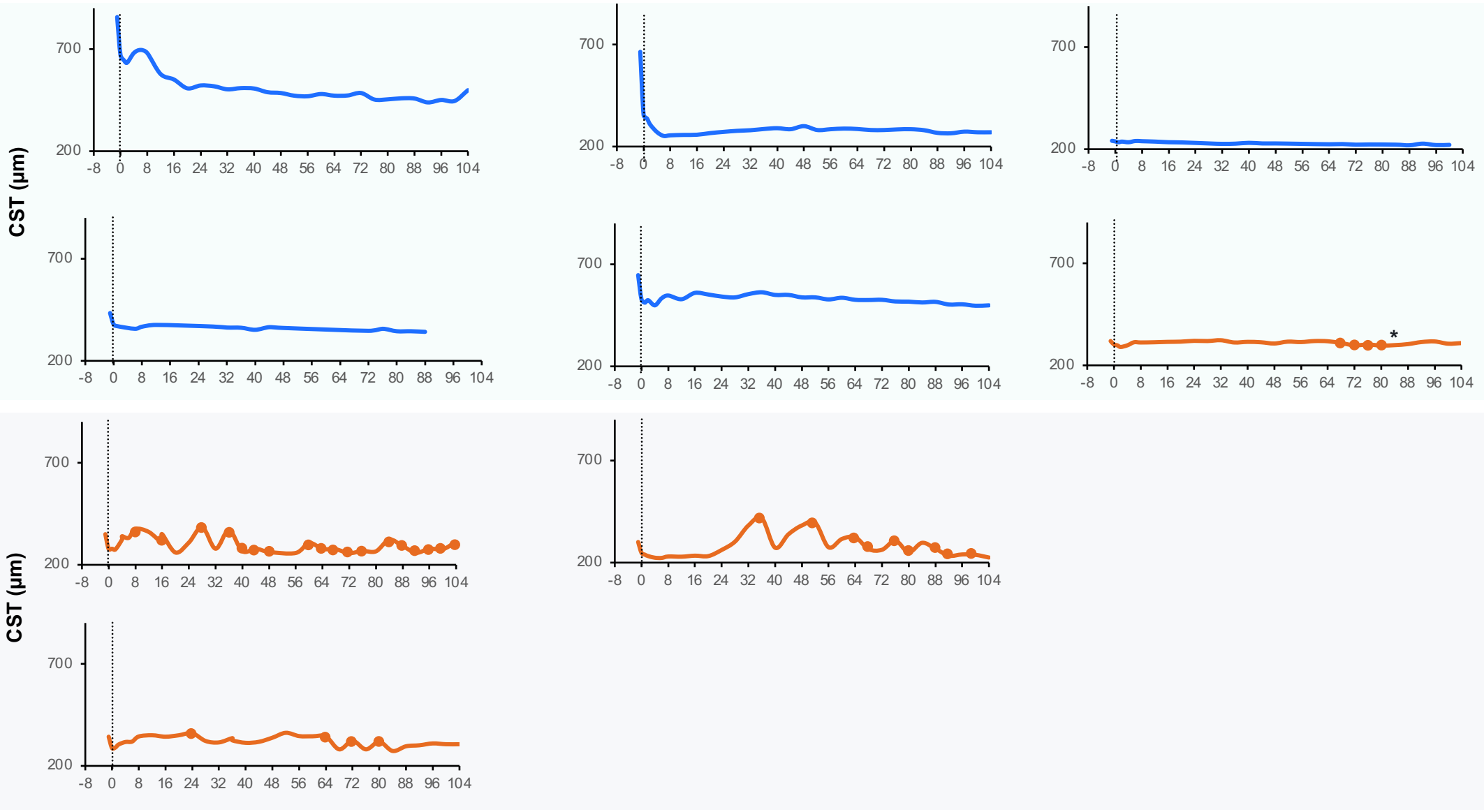
OPTIC Cohort 3: Participants Receiving 2x10^{11} With NAbs <1:125 Demonstrated Rapid Improvement in CST With Minimal Fluctuation

Baseline NAbs <1:125

Baseline NAbs ≥1:125



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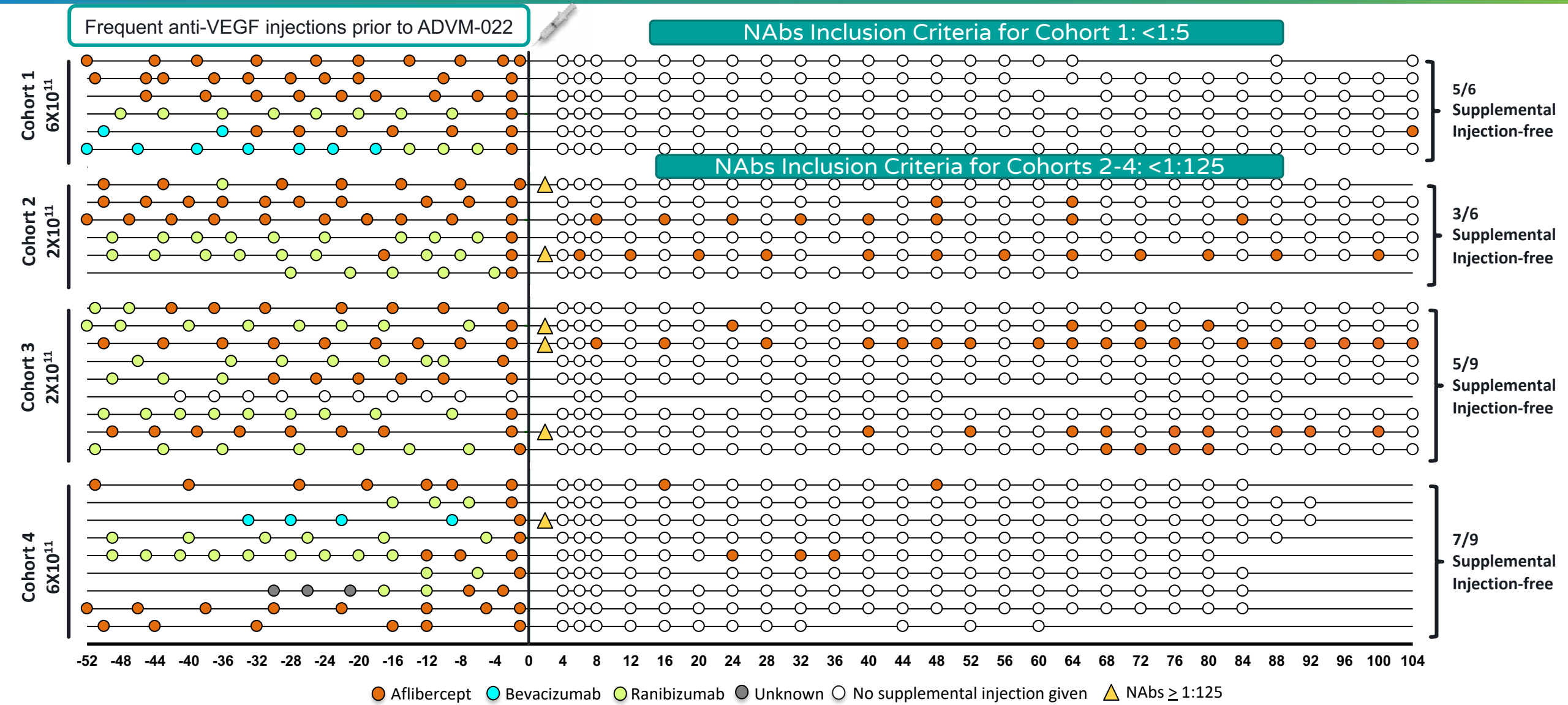
Potential Impact of NAbs on Supplemental Aflibercept Injections



Six patients were diagnosed <1 year prior to ADVM-022 injection: one each in Cohorts 1, 2 and 3, three in Cohort 4. Cohort 2, Patient 1 death due to cardiopulmonary arrest due to hypoxia; *Cohort 2, Patient 6 death due to lung malignancy; Incomplete prior data for Cohort 4, Patient 2. Cohort 4, Patient 4 had a port delivery system (PDS) implanted 3 years prior to Screening (explanted 1.5 years later); Cohort 4, Patient 5 received in a clinical trial not yet unmasked (NCT03790852); IVT, intravitreal injection; Nab, neutralizing antibody*

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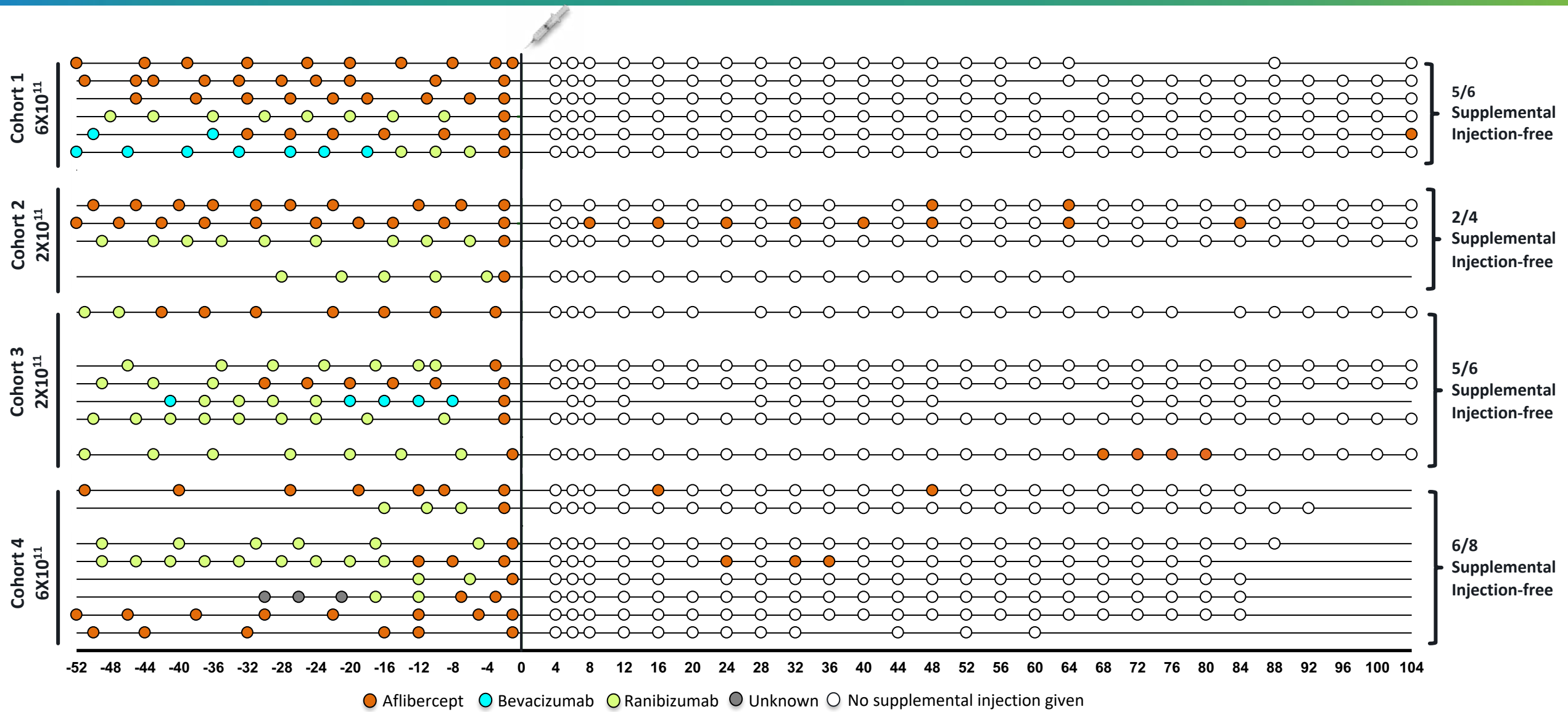
Potential Impact of NAbs on Supplemental Aflibercept Injections: NAbs <1:125 Only



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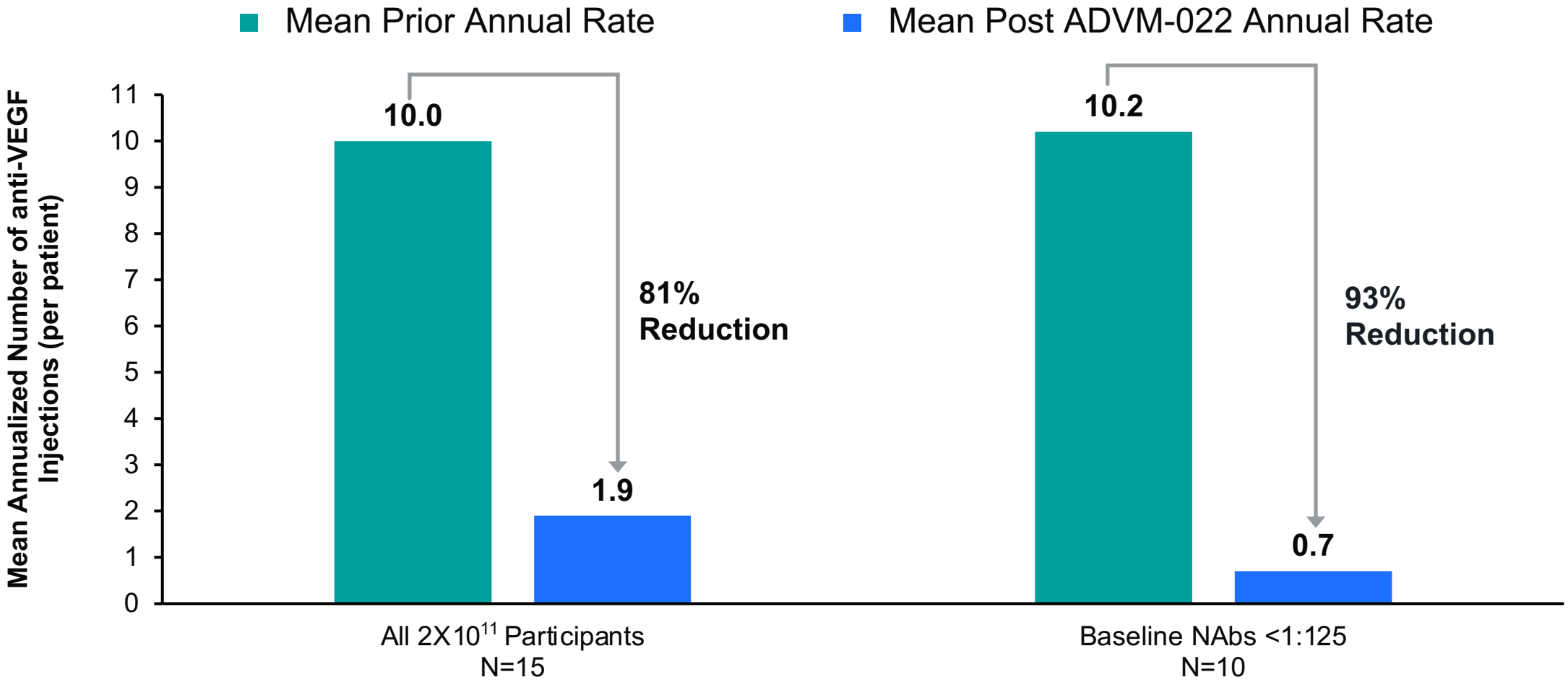
93% Reduction in Annualized Anti-VEGF Injections in ADVM-022 $2x10^{11}$ Participants With NAbs <1:125

$2x10^{11}$ vg/eye All Participants[a] vs Participants With Baseline NAbs <1:125



[a]Only one patient in the high-dose cohort ($6x10^{11}$ vg/eye) had baseline NAbs ≥1:125. A 98% reduction in annualized anti-VEGF Injections was observed in the $6x10^{11}$ group.
Annualized rate (Prior) = (number of IVTs in 12 months prior to ADVM-022) / (days from the first IVT in the past 12 months to ADVM-022 / 365.25).
Annualized rate (Post) = (numbers of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25).
NAb, neutralizing antibody; VEGF, vascular endothelial growth factor.

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Safety Summary

- All inflammation observed at the $2x10^{11}$ vg/eye dose was responsive to topical corticosteroids
  - No participants in the $2x10^{11}$ vg/eye cohorts required any topical corticosteroids to treat inflammation at most recent follow-up
- Across all cohorts, most ADVM-022-related ocular AEs were mild (84.1%) to moderate (16.7%)
  - One SAE of uveitis occurred in cohort 1 ($6x10^{11}$ vg/eye dose) which was responsive to topical corticosteroids
- No vasculitis, retinitis, choroiditis, vascular occlusions or endophthalmitis
- No clinically relevant low IOP events observed at either dose
- No evidence of correlation between baseline NAbs and occurrence of inflammation or other safety events has been observed
- ADVM-022 was well tolerated in the nAMD population studied in OPTIC

SAE, serious adverse event.

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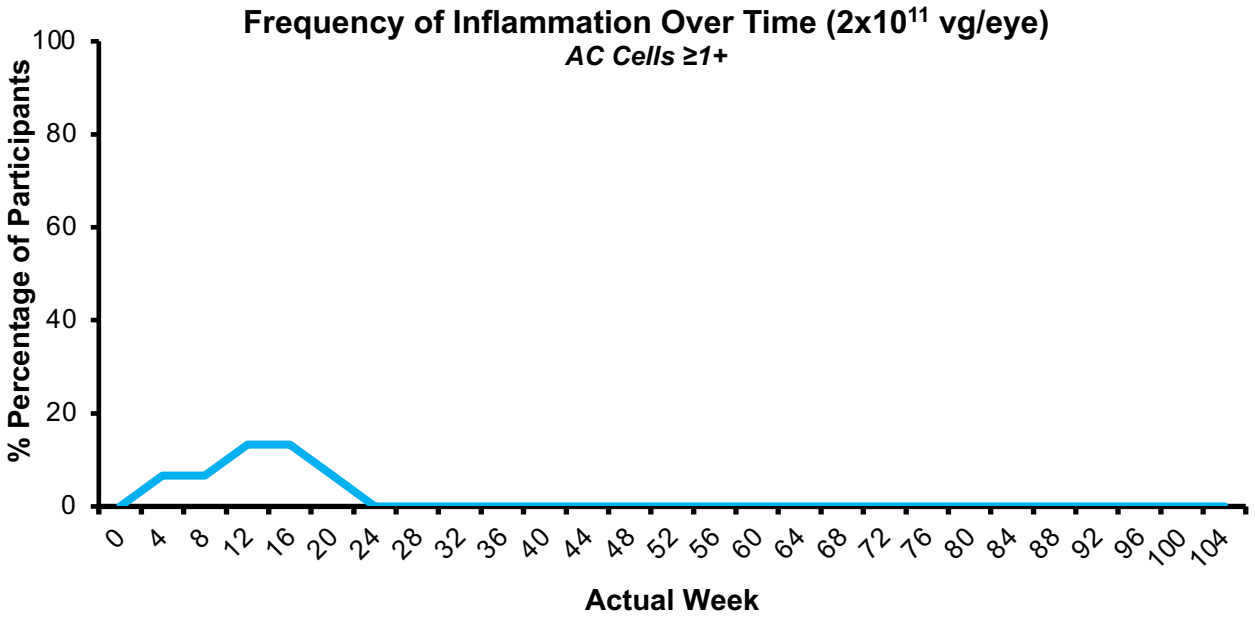
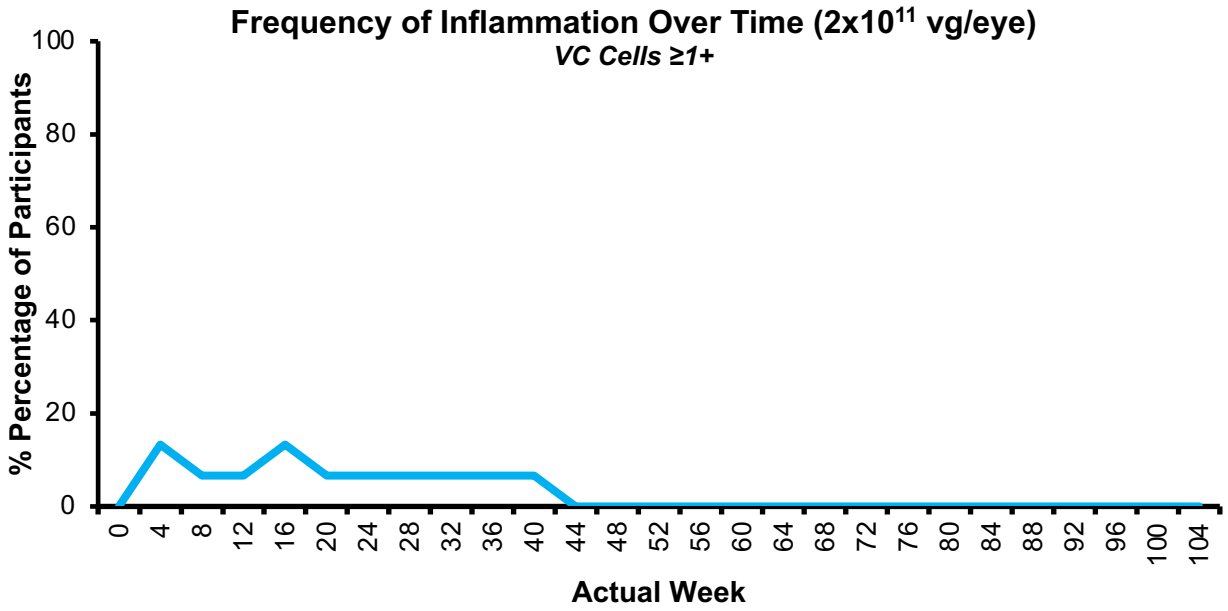
Frequency of Inflammation Decreases Over Time





AC, aqueous cells; SAE, serious adverse event; VC, vitreous cells.
‡One AE of moderate recurrent uveitis deemed to be related to ADVM-022 was responsive to steroid eye drops (Cohort 1).
Cell grades as assessed by slit lamp, Grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria for aqueous cells and National Institutes of Health guidelines for vitreous cells.
AC: 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 cells; VC: 0.5+: 1-10 cells 1+: 11-20 cells 2+: 21-30 cells 3+: 31-100 cells 4+: >100 cells; Rare cells are captured as 0.5+ for this analysis

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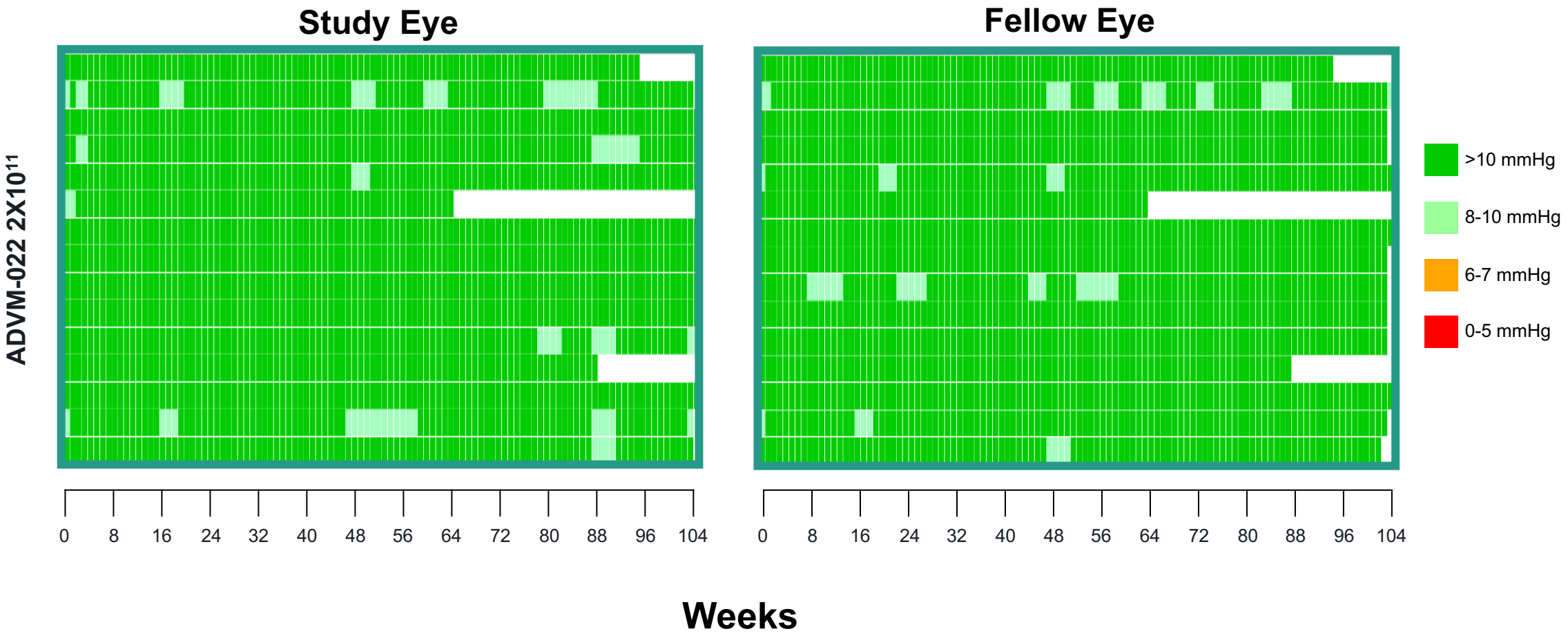
No Effect on IOP Observed in the $2x10^{11}$ vg/eye Dose Group Through 2 Years



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Summary: $2x10^{11}$ vg/eye Dose Safe and Effective with Duration of Action Out to 2.5 Years

- 80% of OPTIC participants had NAbs <1:125
- Participants with NAbs <1:125 demonstrate better efficacy:
  - Higher aflibercept levels with sustained expression
  - Marked improvement in CST with fewer fluctuations
  - 93% reduction in mean annualized anti-VEGF injection rate
- ADVM-022 was well tolerated in the OPTIC study, with no participants in the $2x10^{11}$ dose group requiring corticosteroid drops for the treatment of inflammation at most recent follow up
- The long duration of protein expression, efficacy, and favorable safety profile support the further development of the $2x10^{11}$ dose as well as a lower $6x10^{10}$ dose in nAMD

Data Cut: Feb 24, 2022

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