ADVM-022 (ixoberogene soroparvovec) Intravitreal Gene Therapy for Neovascular AMD: Phase 1 OPTIC Trial Update

Dante Pieramici, MD

– On behalf of the OPTIC investigators –

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Disclosures

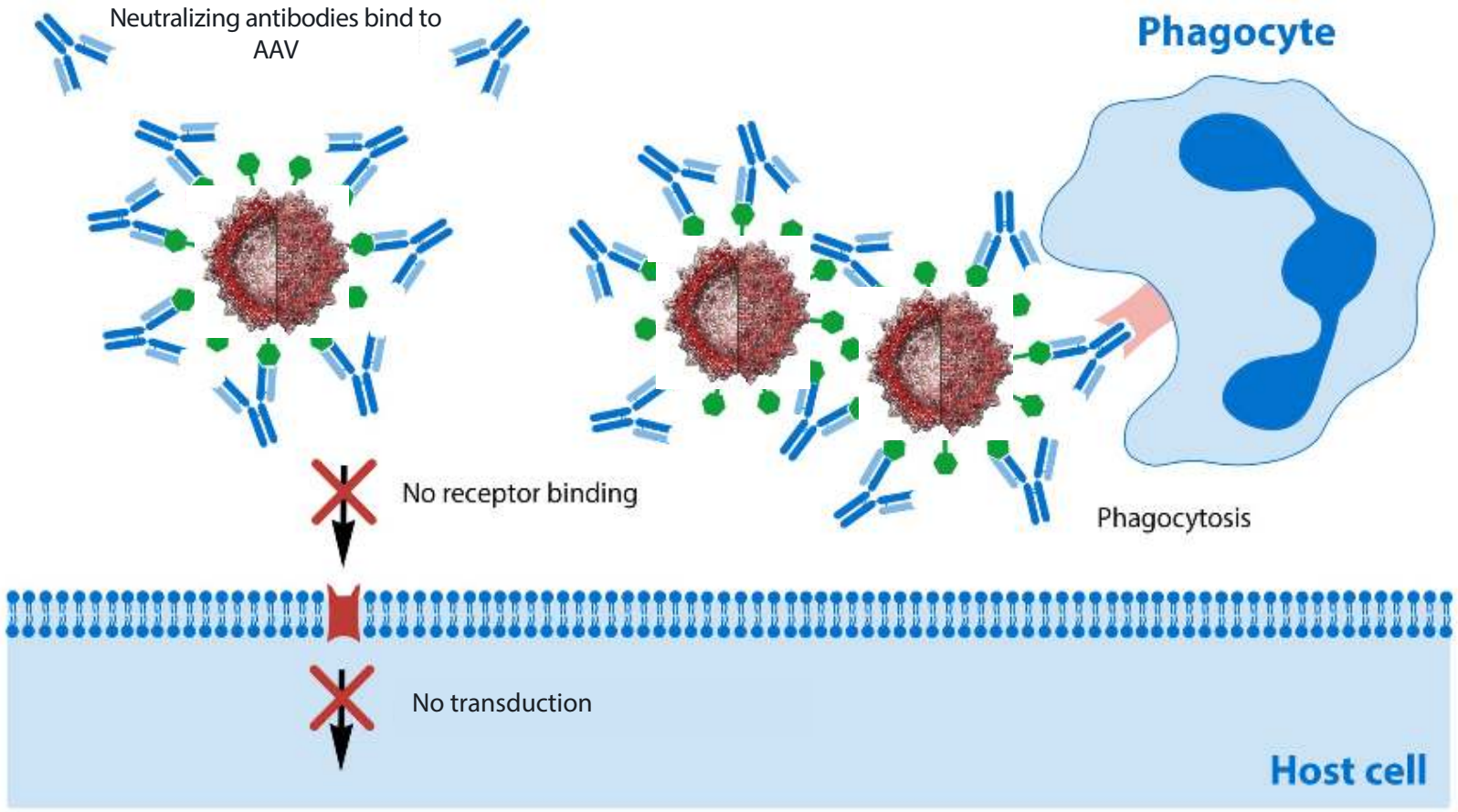
- Consultant/Advisory: Genentech, Regeneron, RegenXBio, **Adverum**, Gemini, NGM, IVERIC, Unity
- Research Funding: Genentech, Regeneron, RegenXBio, **Adverum**, Gemini, NGM, Stealth, Unity, Apellis, Novartis, Kodiac, Chengdu Kanghong, IVERIC, Ocular Therapeutix

OPTIC Summary

- IVT ADVM-022 (ixoberogene soroparvovec [ixo-vec]) was well tolerated in the OPTIC Study in nAMD patients, while maintaining to improving visual acuity and retinal anatomy, and reducing treatment burden
- Following ADVM-022 dosing, stable aflibercept expression was sustained through three years in nAMD patients
- Sub-analysis of the OPTIC Study suggests that AAV neutralizing antibody (NAbs) levels may impact viral transduction and subsequent protein expression

ADVM-022 is an investigational gene therapy that is not currently approved by the FDA

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

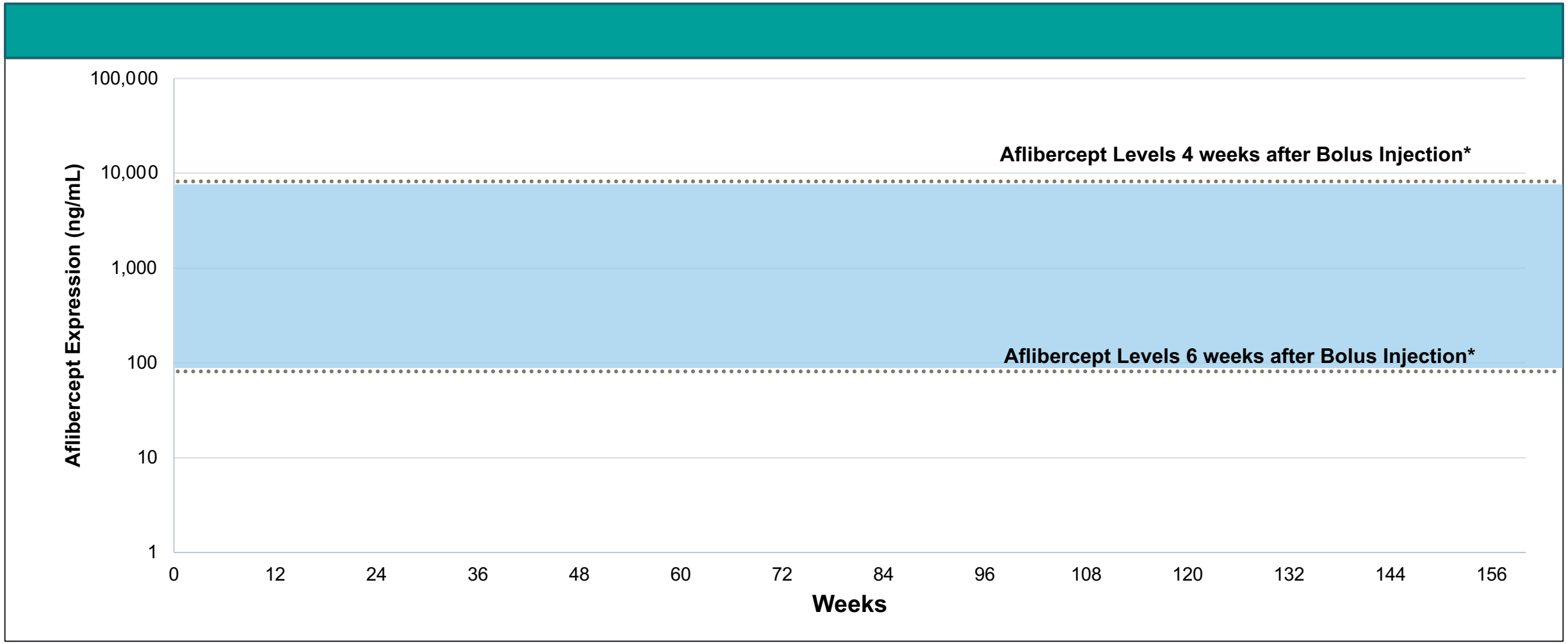
Baseline Characteristics and Participant Status

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) Annualized anti-VEGF Injections Prior to ADVM-022	9.7 (8.4–11.2)	10.5 (8.5–11.7)	9.6 (7.9–12.8)	9.9 (6.3–13)**
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; ***NAbs exclusion criteria were a titer level of >1:5 for cohort 1 and >1:125 for cohorts 2-4*
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 - Comparable to Bolus Aflibercept 4-6 Weeks Post Injection - Sustained Through 3 Years



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

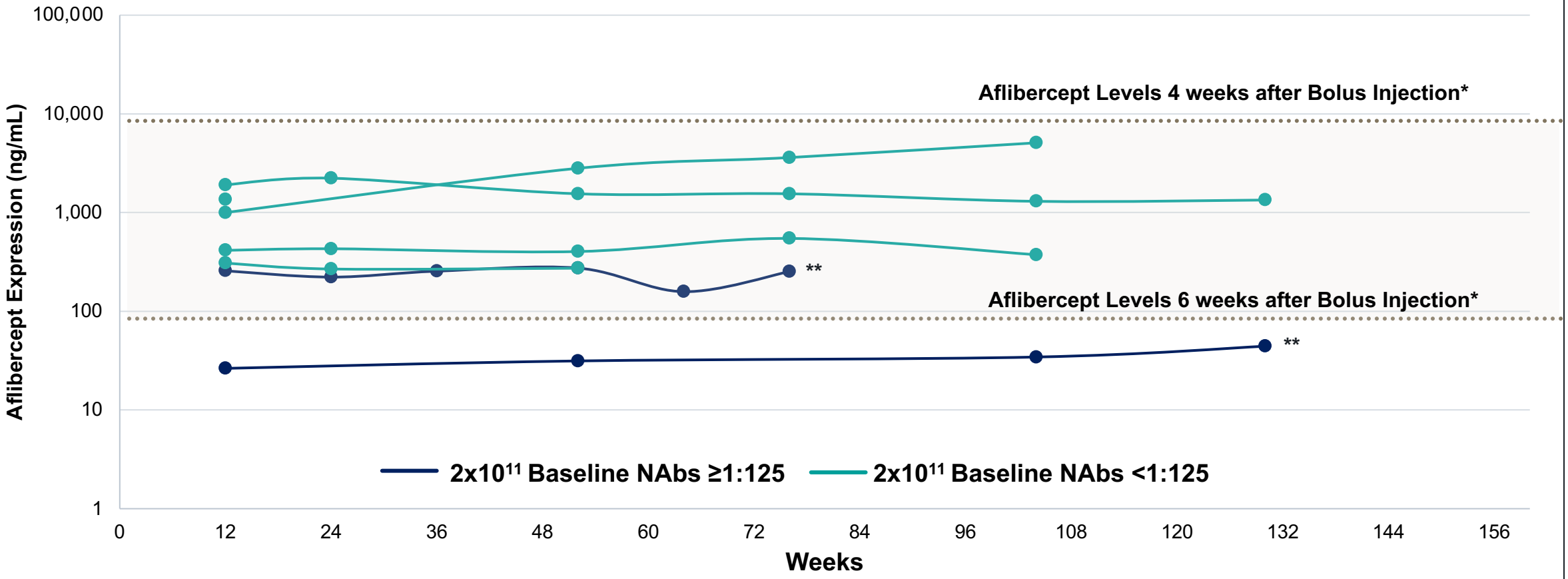
Protocol amendment for aqueous sample collection for participants that consented.

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

ADVM-022 at 2x10^{11} Dose Provides Sustained Therapeutic Aflibercept Expression Through 132 Weeks

Individual Participant Plots: 2x10^{11}



*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.

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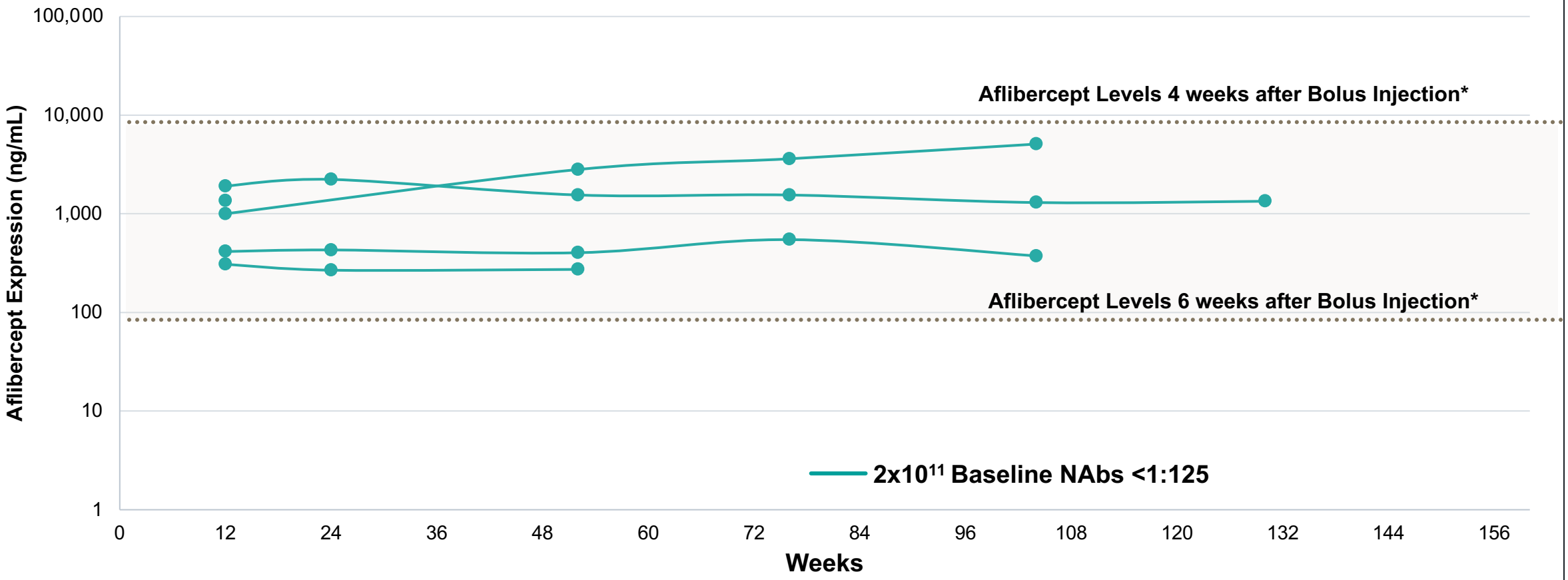
Data Cut: Feb 24, 2022

ADVM-022 at 2x10^{11} Dose Provides Sustained Therapeutic Aflibercept Expression Through 132 Weeks

Individual Participant Plots: 2x10^{11} Minus High NAbs



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Protocol amendment for aqueous sample collection for participants that consented.

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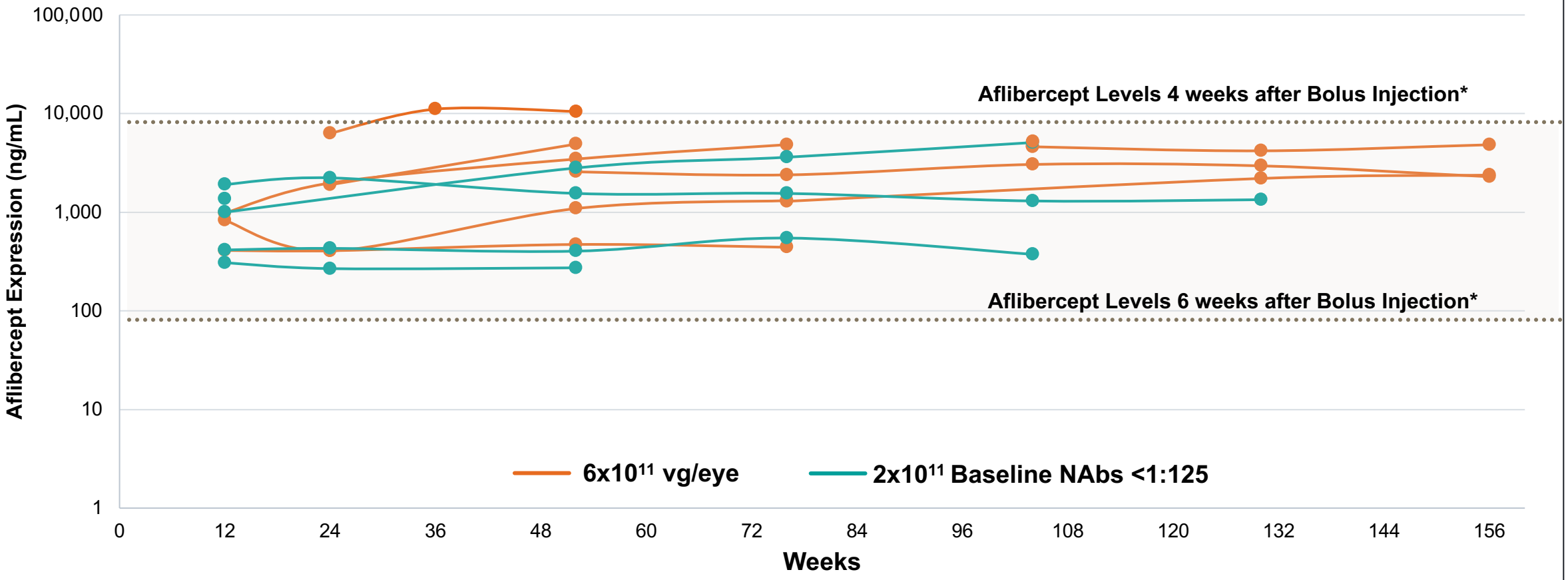
Data Cut: Feb 24, 2022

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

Individual Participant Plots: $2x10^{11}$ (low NAbs) and $6x10^{11}$



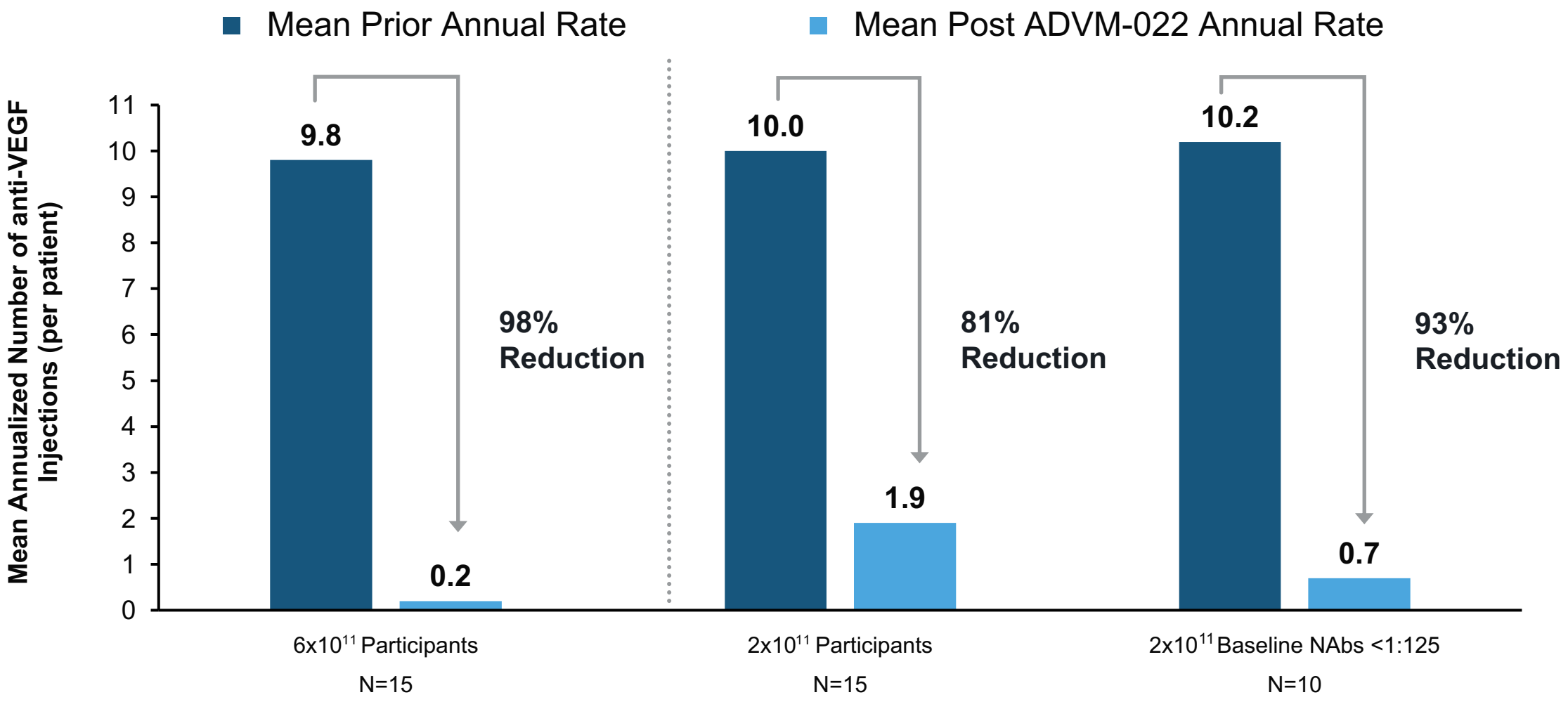
*Modeled based on Do et al. Retina 2020; 40:643-647.

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

ADVM-022 2x10^{11} vg/eye With NAbs <1:125 Provides Comparable Reduction in Annualized Anti-VEGF Injections to 6x10^{11} vg/eye

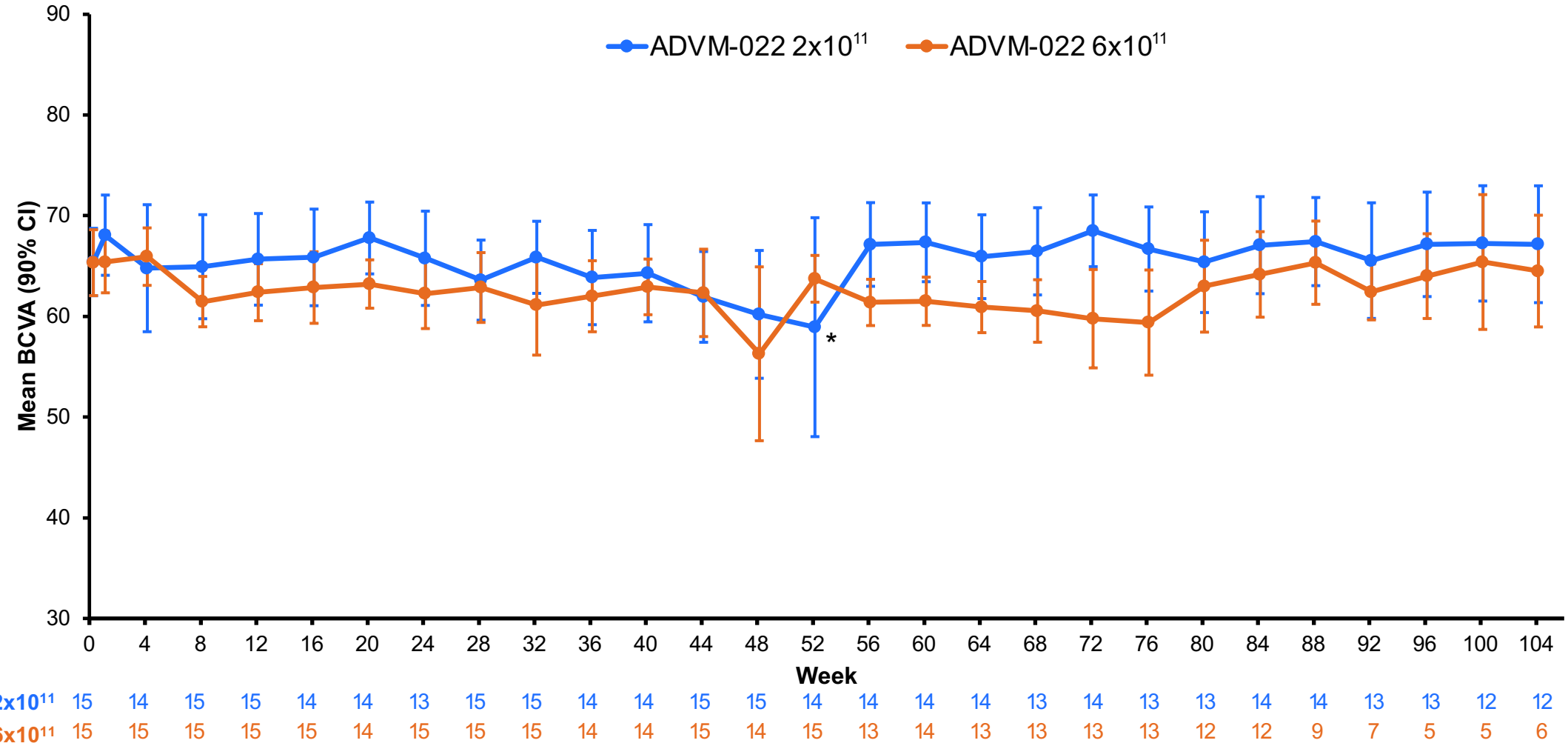


Annualized rate (Prior) = (number of IVTs in 12 months prior to ADVM-022) / (days from the first IVT in the past 12 months to ADVM-022 / 365.25).
Annualized rate (Post) = (numbers of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25).
NAb, neutralizing antibody; VEGF, vascular endothelial growth factor.

Data Cut: Feb 24, 2022

BCVA Maintained Over Time Across Both Dose Groups

Mean BCVA (90% CI) by Cohort And Week



Mean BCVA (letters) change from baseline to last visit (90% CI)

+0.2 (-4.6, 5.0)
2x10^11 vg/eye

+0.3 (-2.5, 3.2)
6x10^11 vg/eye

p = 0.967**

**Cataract surgery*

***Derived from a two-sample t-test.*

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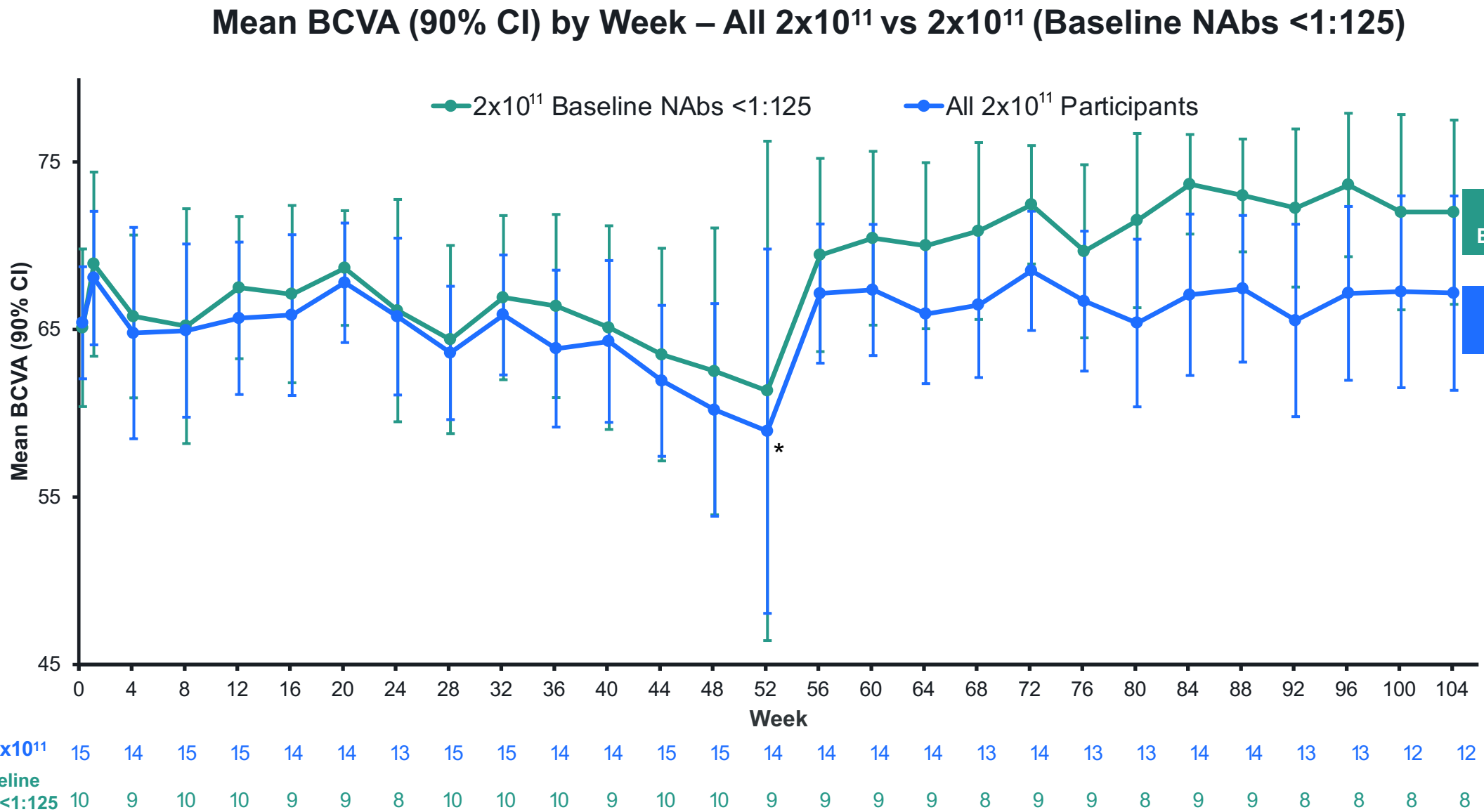
BCVA Maintained Over Time in All Participants Treated With ADVM-022 $2x10^{11}$ vg/eye and Improved in Those With Baseline NAbs <1:125



Mean BCVA (letters) change from baseline to last visit (90% CI)

+5.2 (2.1, 8.3)
Baseline NAbs <1:125

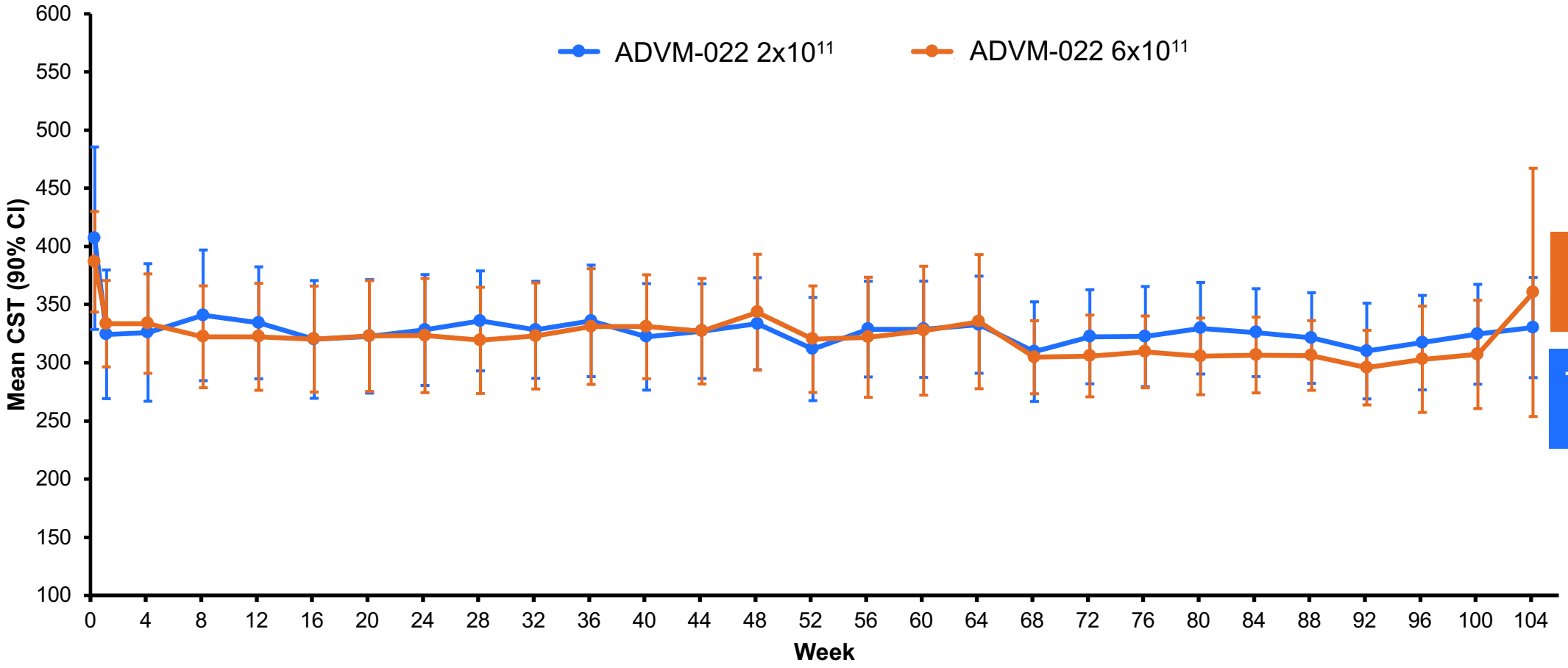
+0.2 (-4.6, 5.0)
All $2x10^{11}$ vg/eye

**Cataract surgery*

Data Cut: Feb 24, 2022

Mean CST Significantly Reduced at Both Doses

Mean CST (90% CI) by Cohort And Week



2x10^11	15	14	15	15	14	14	13	15	15	14	14	15	15	12	13	13	14	13	14	13	13	14	14	13	13	12	11
6x10^11	15	15	15	15	15	14	15	15	15	14	14	14	13	15	13	13	12	13	12	13	12	12	8	6	5	5	6	

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

-55.7 (-90.6, -20.8)
p = 0.014*
6x10^11 vg/eye

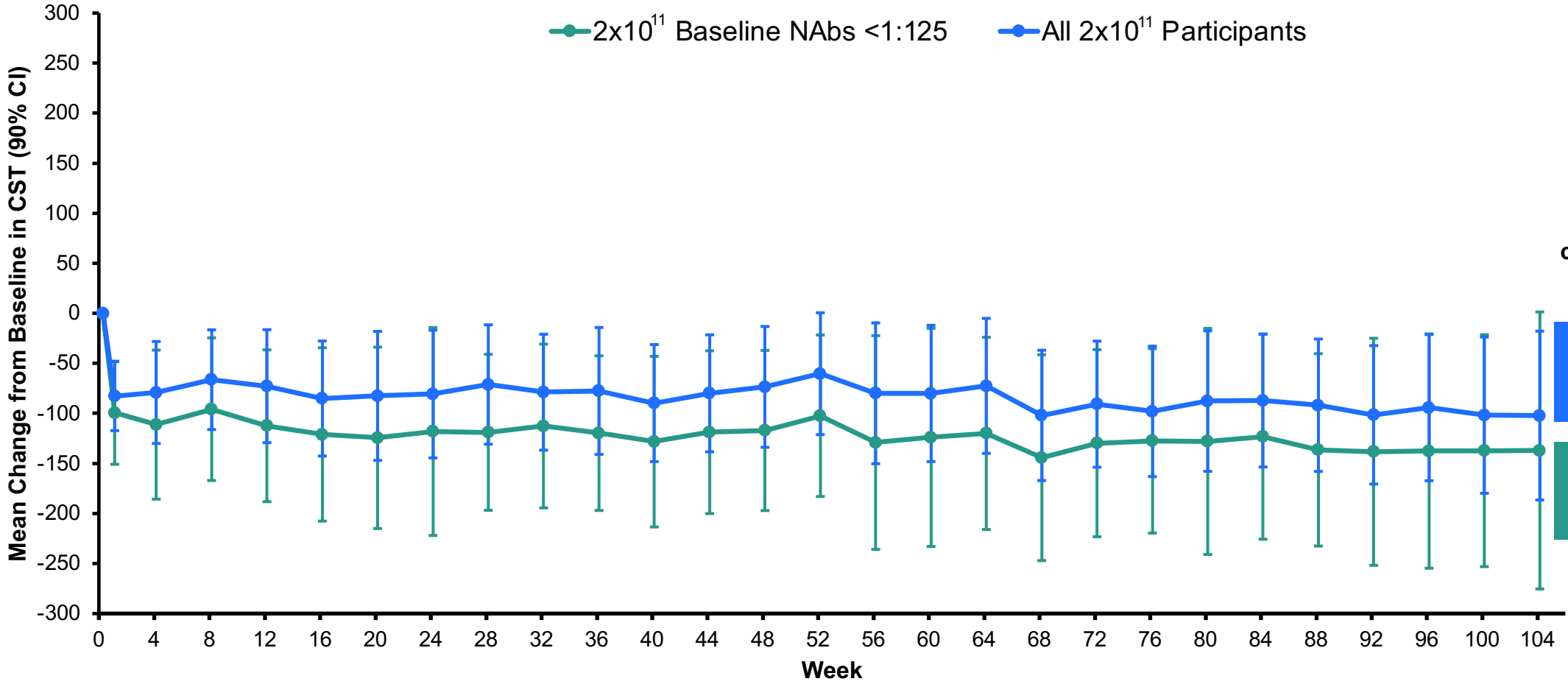
-95.9 (-156.5, -35.3)
p = 0.015*
2x10^11 vg/eye

**Derived from a two-sample t-test.*

Data Cut: Feb 24, 2022

Mean CST Significantly Reduced Following ADVM-022 2x10^{11} vg/eye and Maintained Through Two Years

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
All 2x10^{11}	15	14	15	15	14	14	13	15	15	14	14	15	15	12	13	13	14	13	14	13	13	14	14	13	13	12	11
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

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

-95.9 (-156.5, -35.3)
p = 0.015*
All 2x10^{11} vg/eye

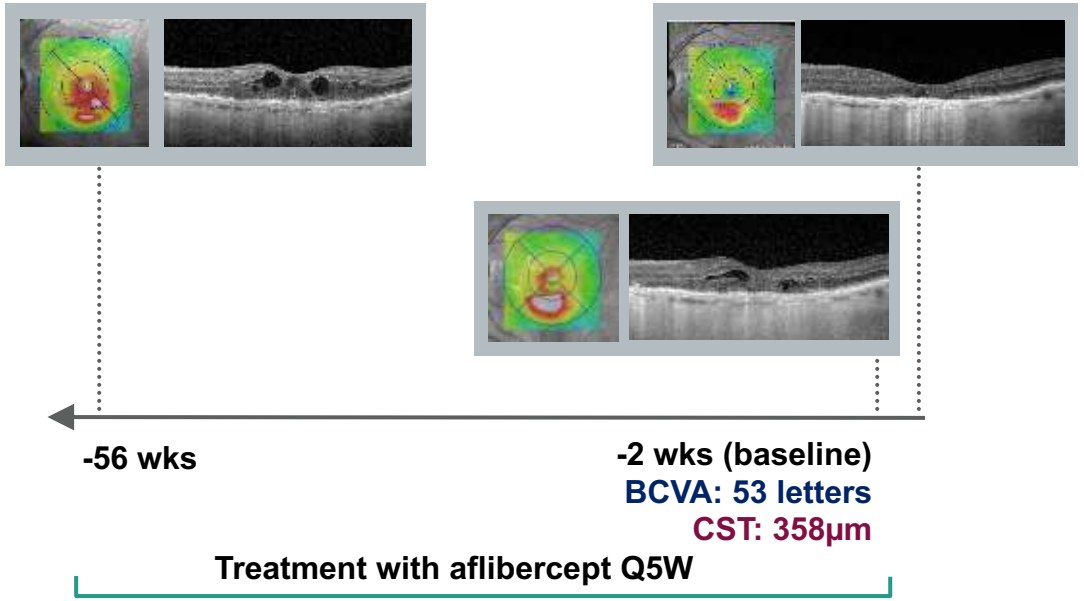
-126.6 (-216.7, -36.5)
p=0.030*
Baseline NAbs <1:125

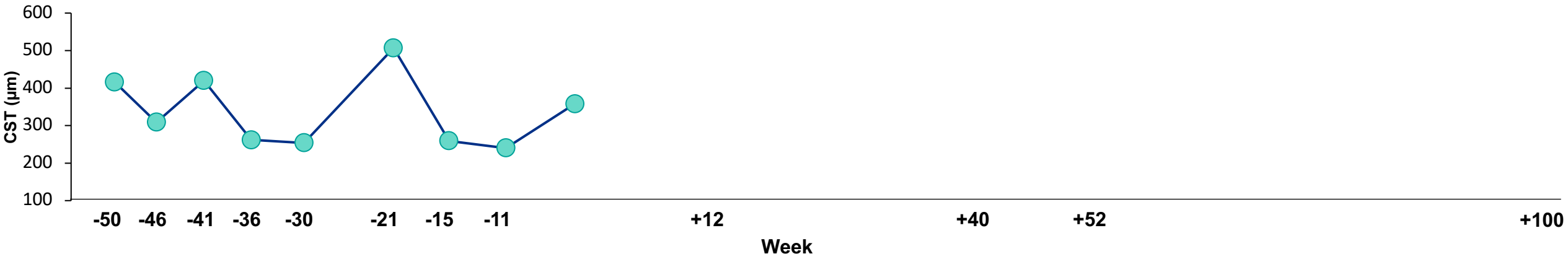
**Derived from a paired t-test comparing mean CST pre-ADVM-022 and at the last visit post-ADVM-022*

Data Cut: Feb 24, 2022

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

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

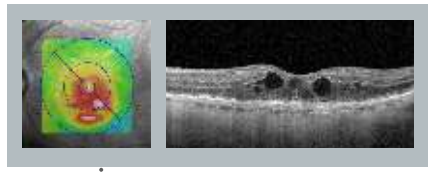
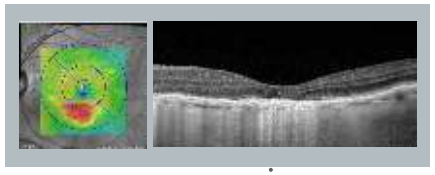
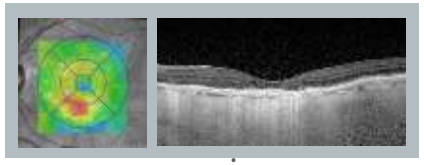
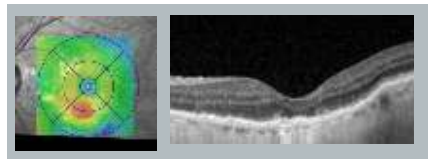
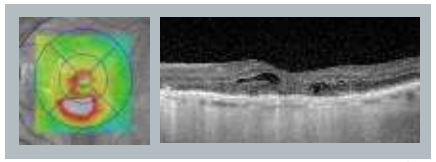
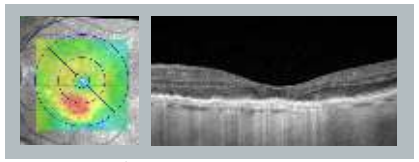
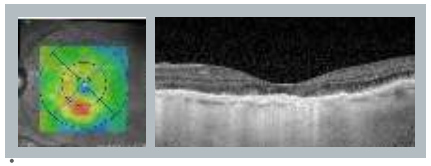




Data Cut: Feb 24, 2022

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

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

-56 wks

-2 wks (baseline)
BCVA: 53 letters
CST: 358µm

Day 0
ADVM-022

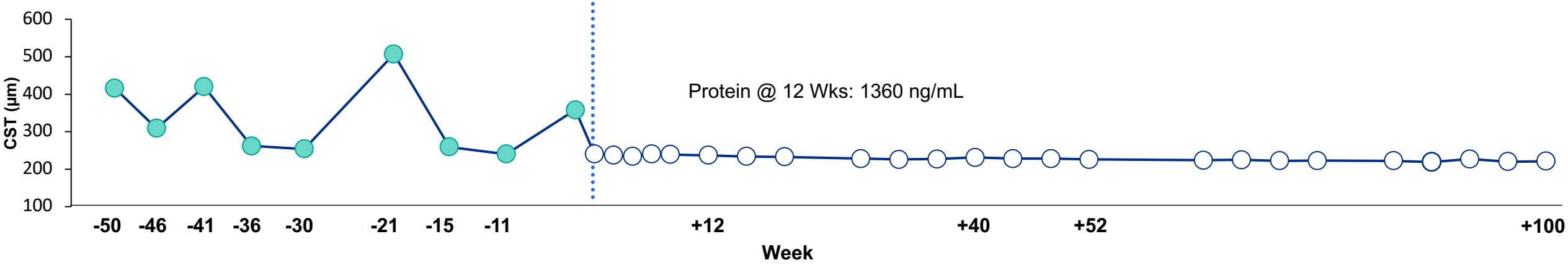
+12 wks
BCVA: +13 letters
CST: -121µm

+40 wks
BCVA: +18 letters
CST: -127 µm

+52 wks
BCVA: +16 letters
CST: -132 µm

+100 wks
BCVA: +13 letters*
CST: -137 µm

Treatment with aflibercept Q5W



Anti-VEGF injection CST measurement only, no injection

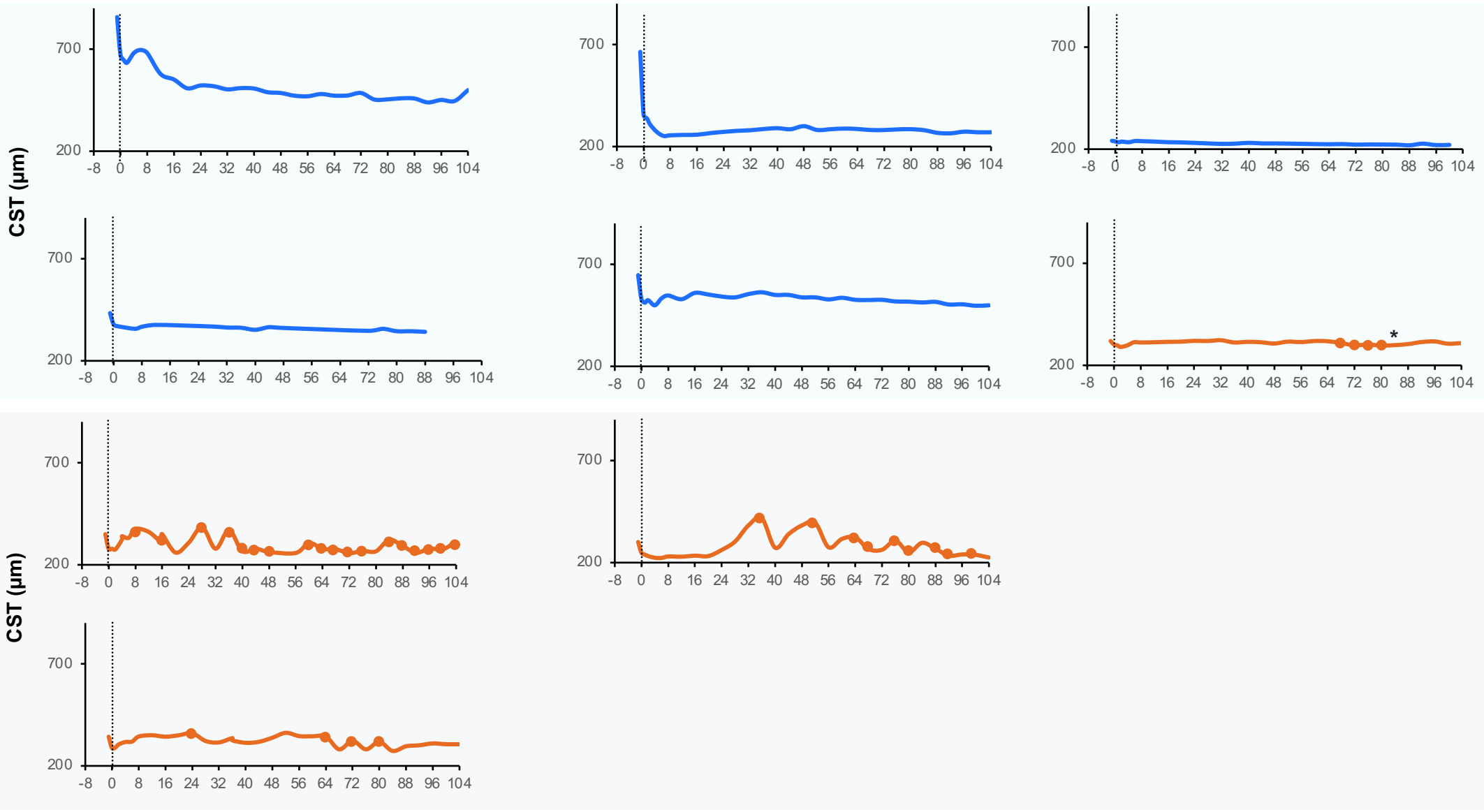
*No CST reading available at week 104. BCVA at week 104 was 58 letters

Data Cut: Feb 24, 2022

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



Data Cut: Feb 24, 2022

Safety Summary

- ADVM-022 was well tolerated in OPTIC, with dose-dependent, mild to moderate* inflammation that 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
- No vasculitis, retinitis, choroiditis, vascular occlusions or endophthalmitis
- No clinically relevant low IOP events observed at either dose
- Across all cohorts, most ADVM-022-related ocular AEs were mild (82.6%) to moderate (16.7%)
  - One SAE related to ADVM-022 (uveitis) occurred in cohort 1 ($6x10^{11}$ dose) at week 76 which was responsive to topical corticosteroids
- No evidence of correlation between baseline NAbs and occurrence of inflammation or other safety events has been observed

AC, aqueous cells; SAE, serious adverse event; VC, vitreous cells.
**Mild inflammation: trace, 0.5+, 1+ and 2+ anterior chamber cell/flare, or trace, 0.5+, 1+ and 2+ vitreous cells; moderate inflammation: +3 anterior chamber cell/flare, or 3+ vitreous cells; severe inflammation: +4 anterior chamber cell/flare, or 4+ vitreous cells*

Data Cut: Feb 24, 2022

OPTIC Conclusions

- Participants had an 81-98% reduction in annualized anti-VEGF injections and demonstrated continuous therapeutic aflibercept protein expression levels through three years
- In both doses, BCVA and CST were maintained to improved through at least two years and CST fluctuations were reduced
- AAV vector transduction and subsequent protein expression may be impacted by the presence of NAbs
- The results from the OPTIC study support the further development of ADVM-022 for nAMD. The Phase 2 LUNA study will evaluate the $2x10^{11}$ vg/eye dose as well as a new, lower $6x10^{10}$ vg/eye dose. The first participant is expected to enroll in Q3 2022

Data Cut: Feb 24, 2022

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