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

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**– On behalf of the OPTIC investigators –**

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# Disclosures

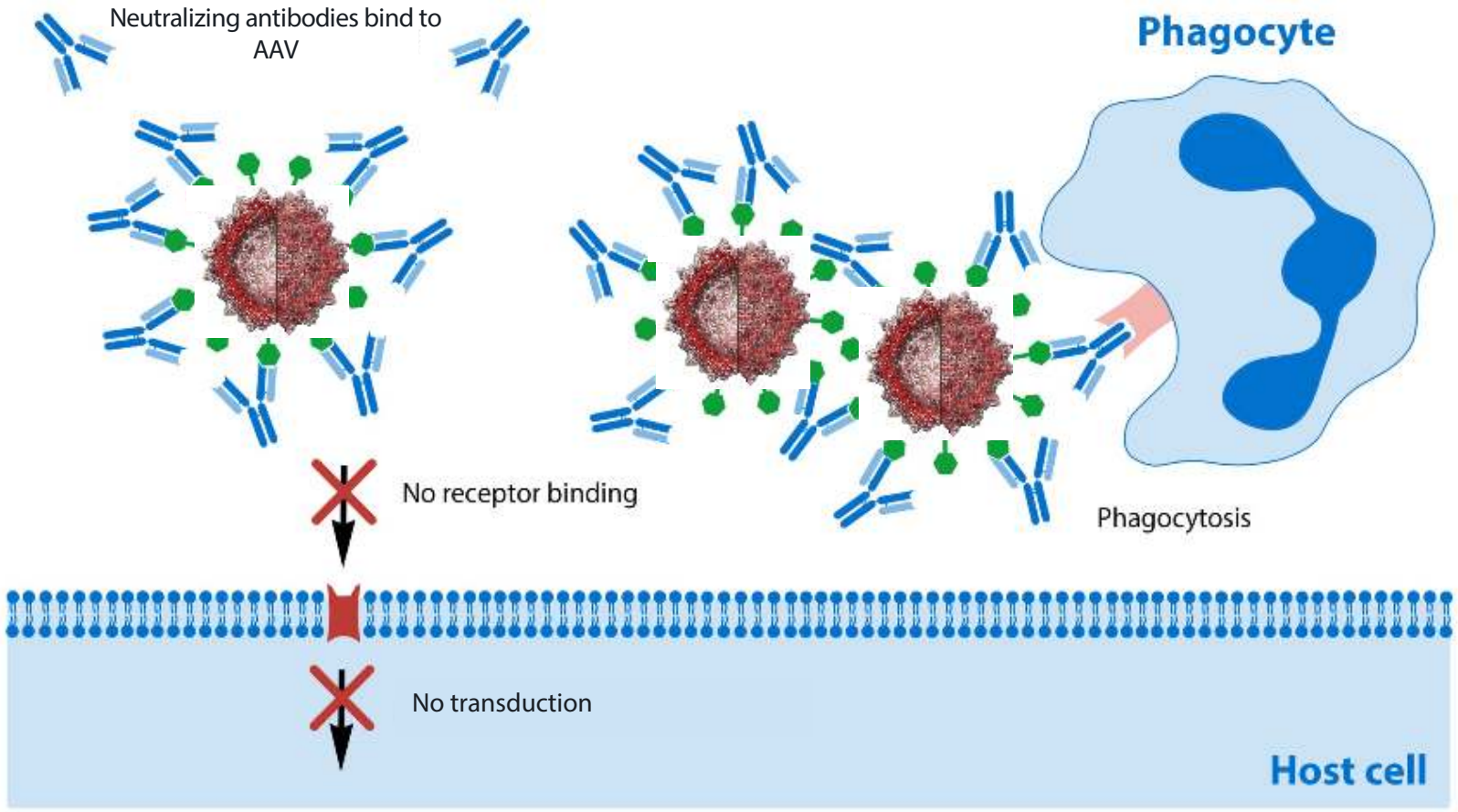
- Consultant/Advisory:  Genentech, Regeneron, RegenXBio, **Adverum**, Gemini, NGM, IVERIC, Unity
- Research Funding:  Genentech, Regeneron, RegenXBio, **Adverum**, Gemini, NGM, Stealth, Unity, Apellis, Novartis, Kodiac, Chengdu Kanghong, IVERIC, Ocular Therapeutix

# 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*

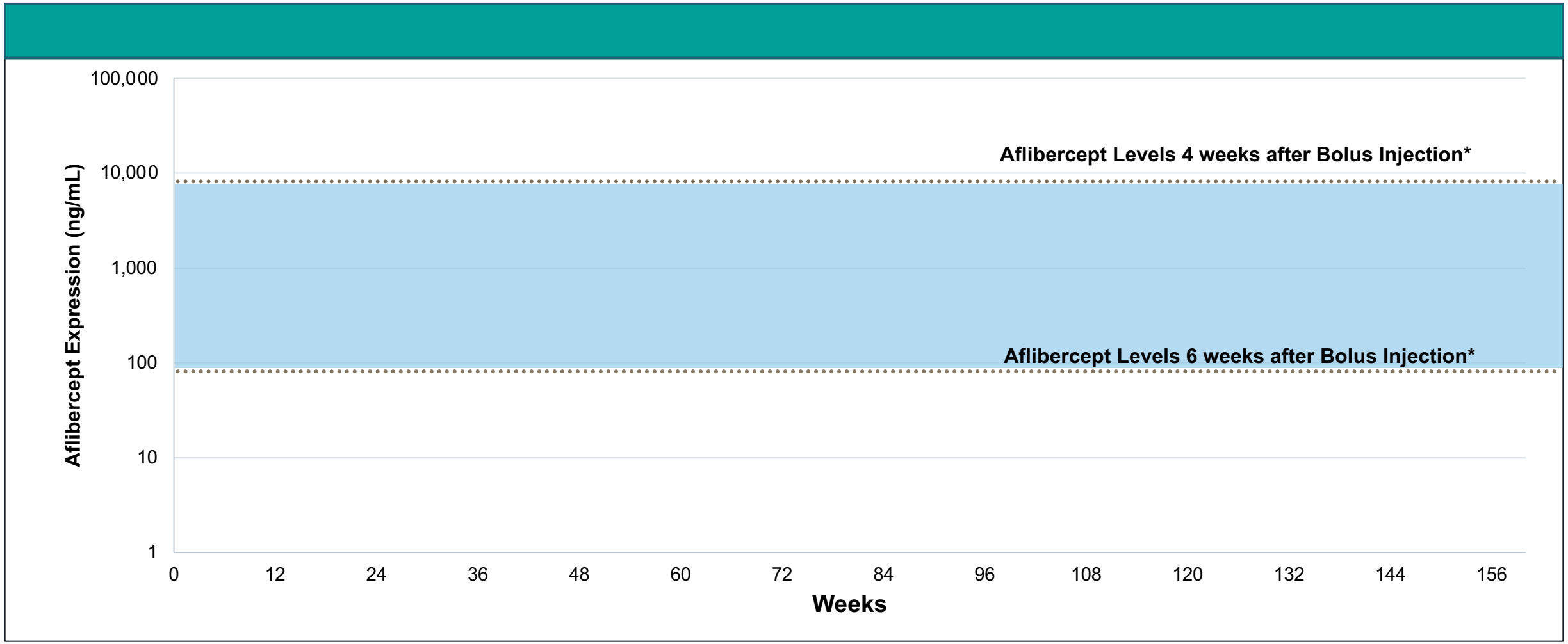
# Baseline Characteristics and Participant Status

| 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.

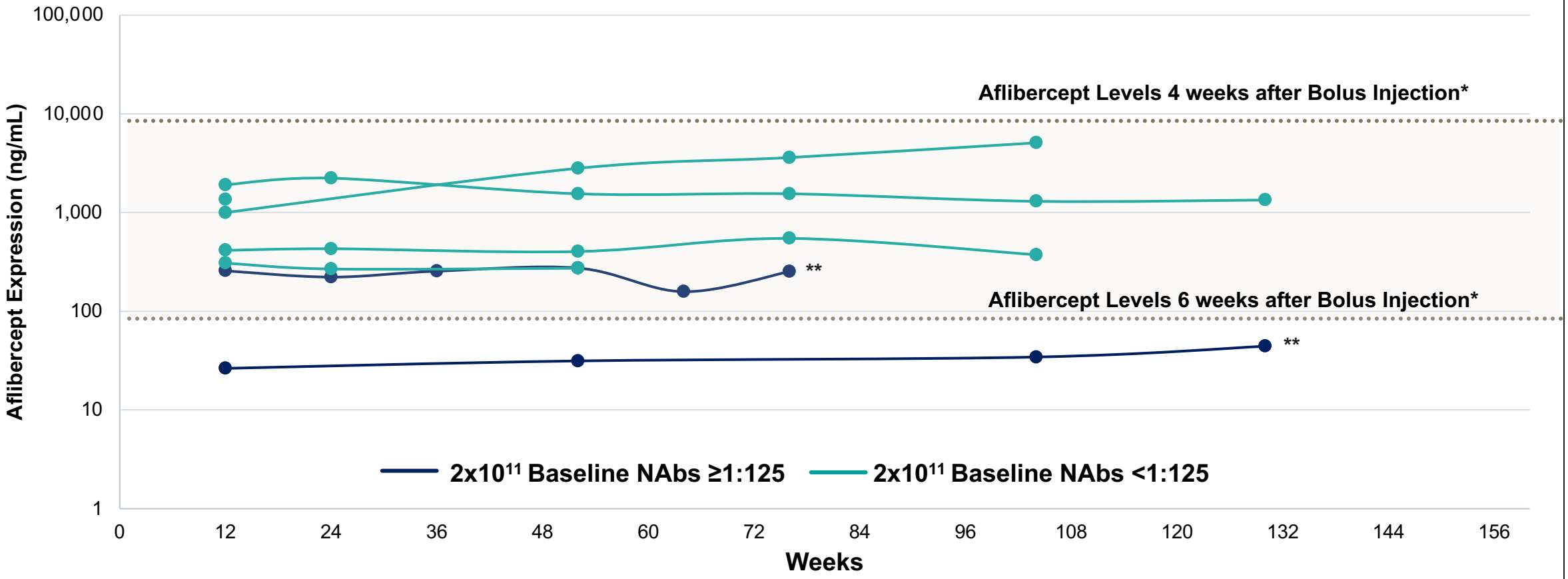
*Protocol amendment for aqueous sample collection for participants that consented.*

*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

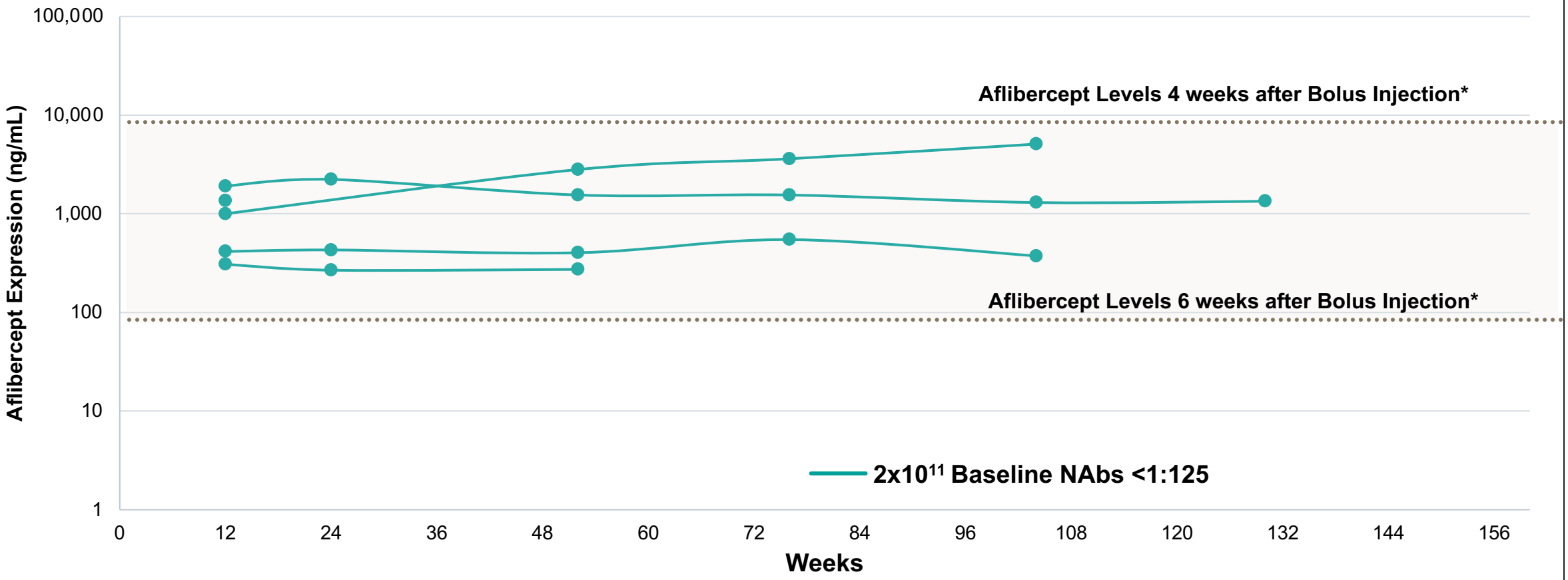
Protocol amendment for aqueous sample collection for participants that consented.

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$^{11}$ Minus High NAbs

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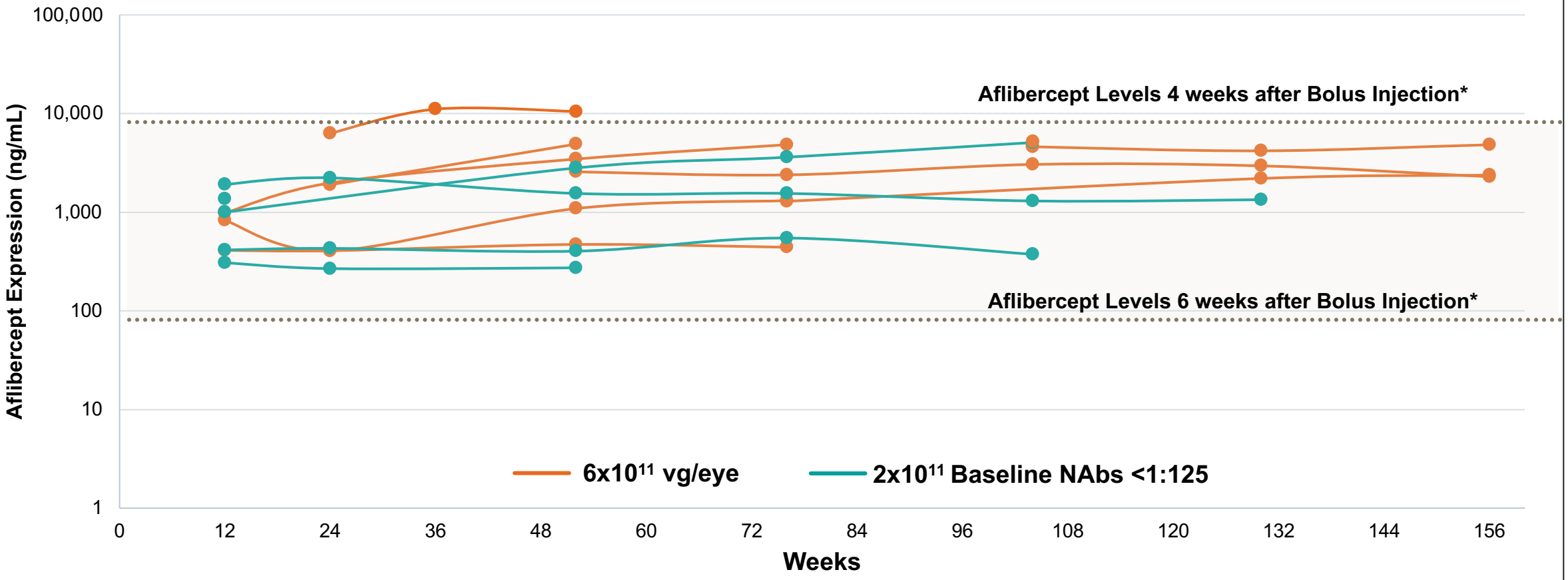
*Data Cut: Feb 24, 2022*

# 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 $6x10^{11}$



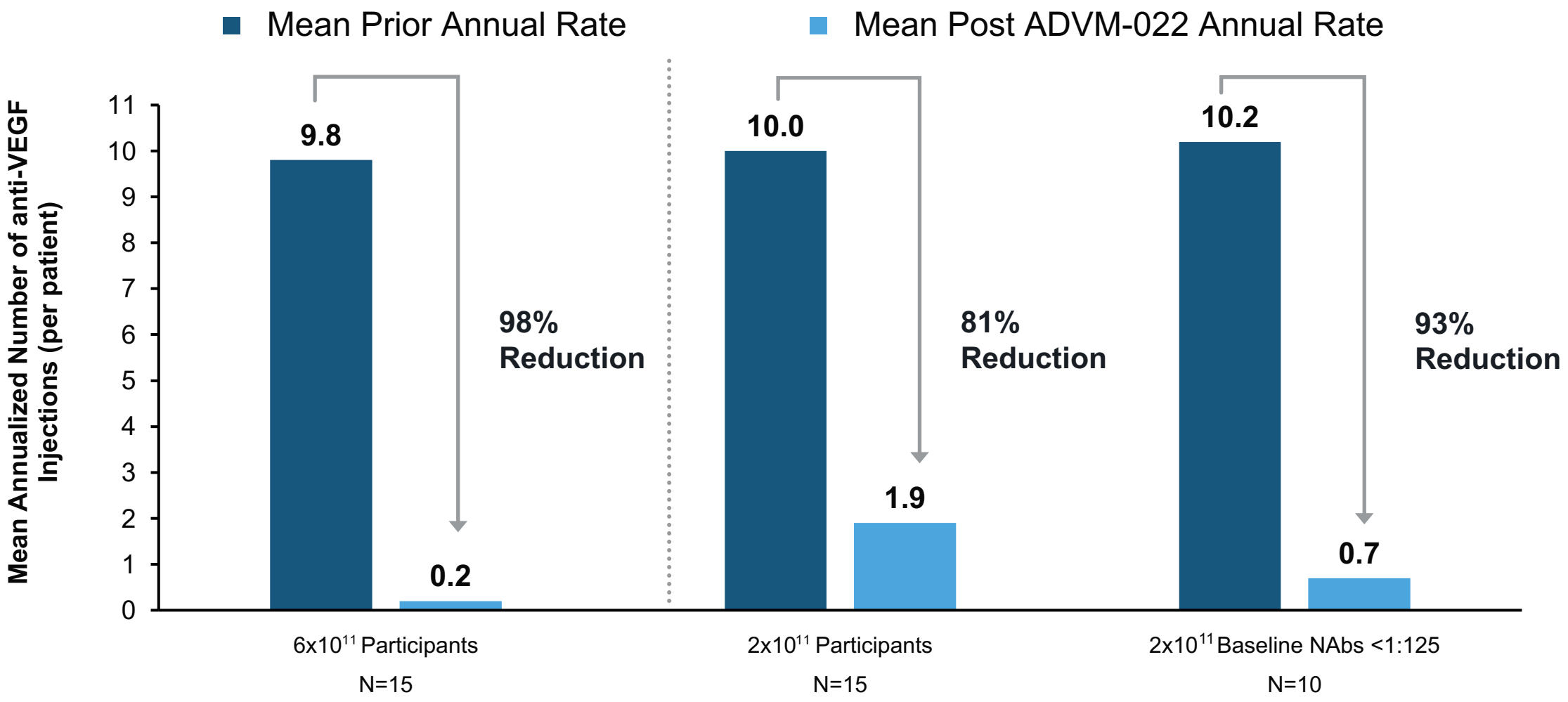

*Modeled based on Do et al. Retina 2020; 40:643-647.

*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

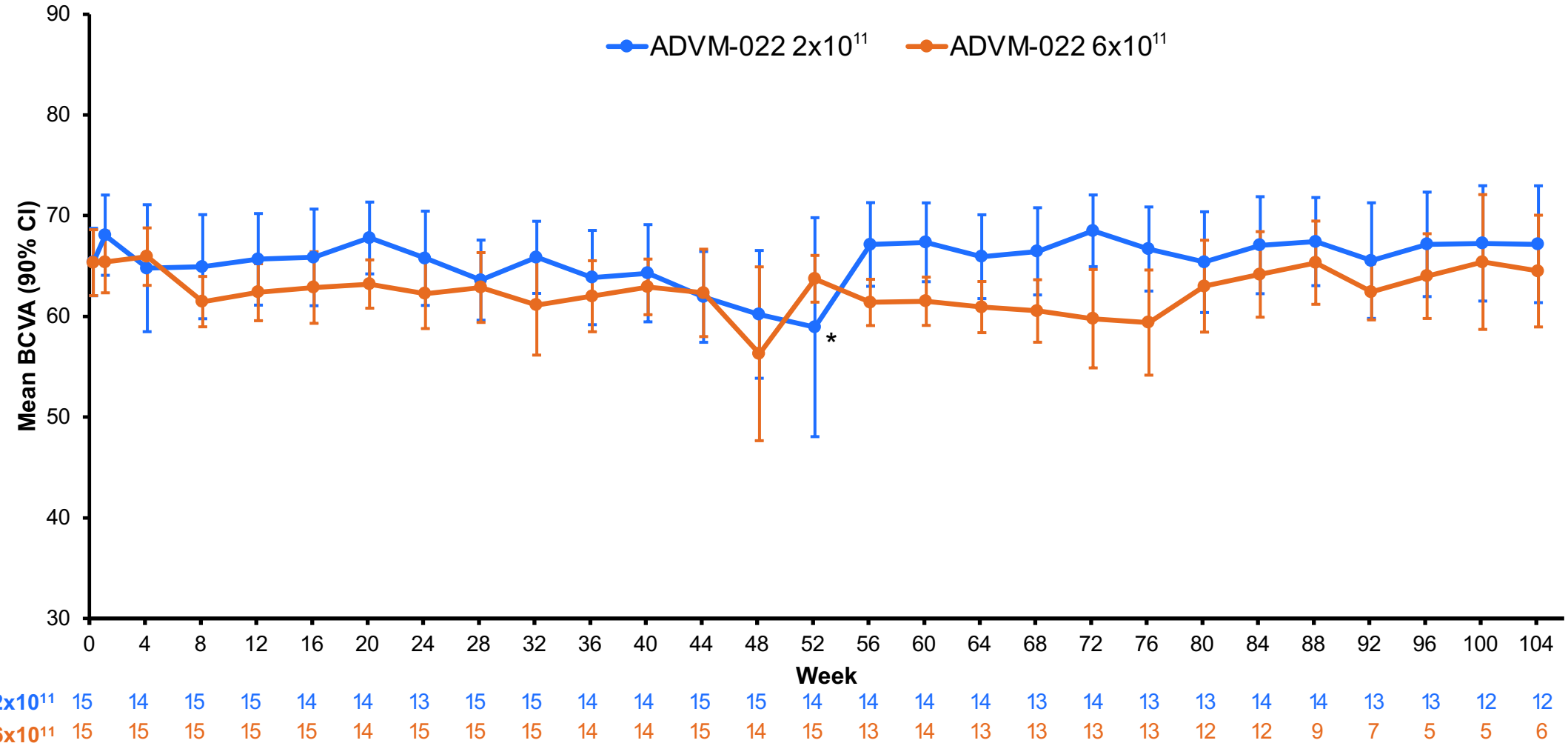



*Annualized rate (Prior) = (number of IVTs in 12 months prior to ADVM-022) / (days from the first IVT in the past 12 months to ADVM-022 / 365.25).*
*Annualized rate (Post) = (numbers of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25).*
*NAb, neutralizing antibody;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

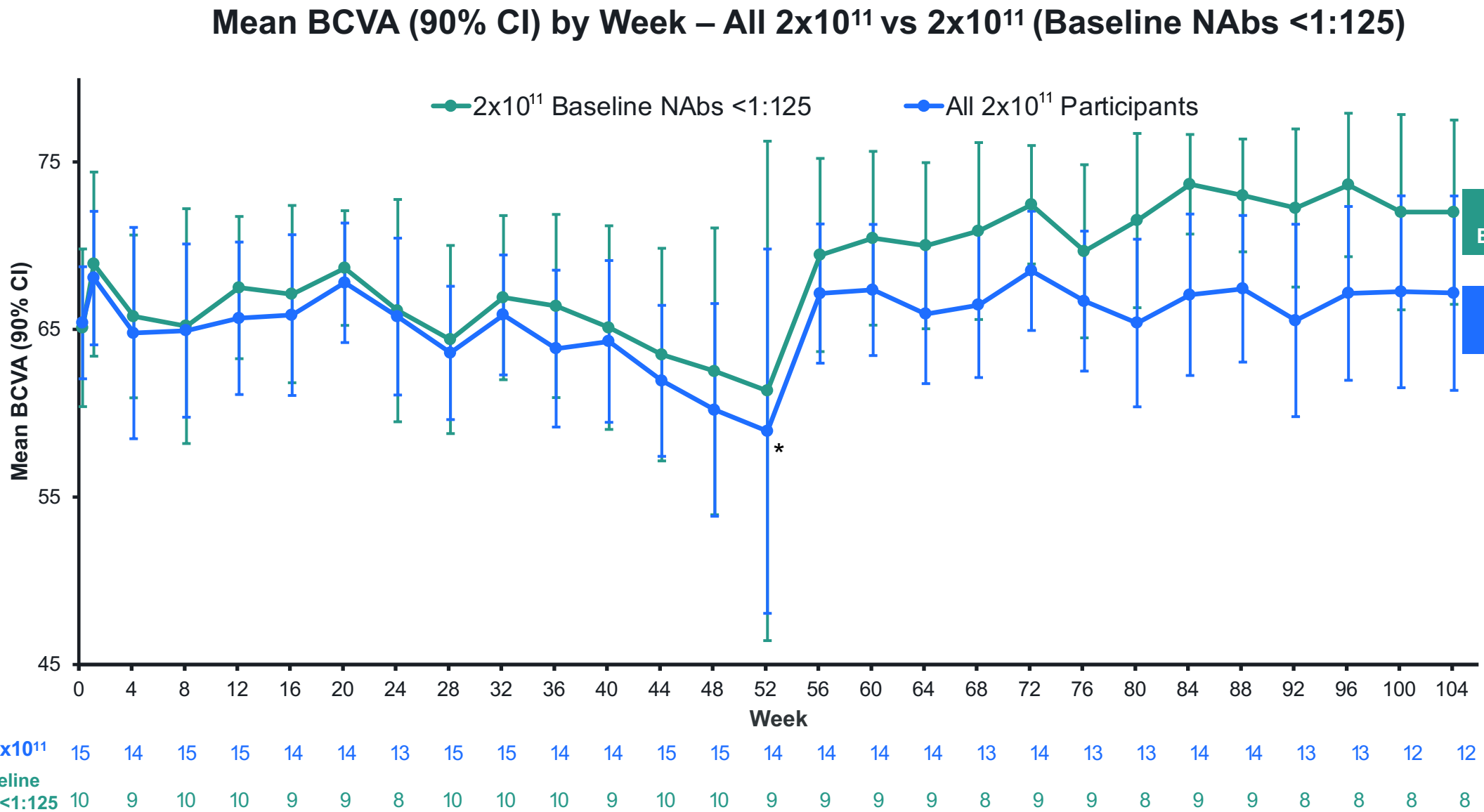
**p = 0.967****

**Cataract surgery*

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

*Data Cut: Feb 24, 2022*

# 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**

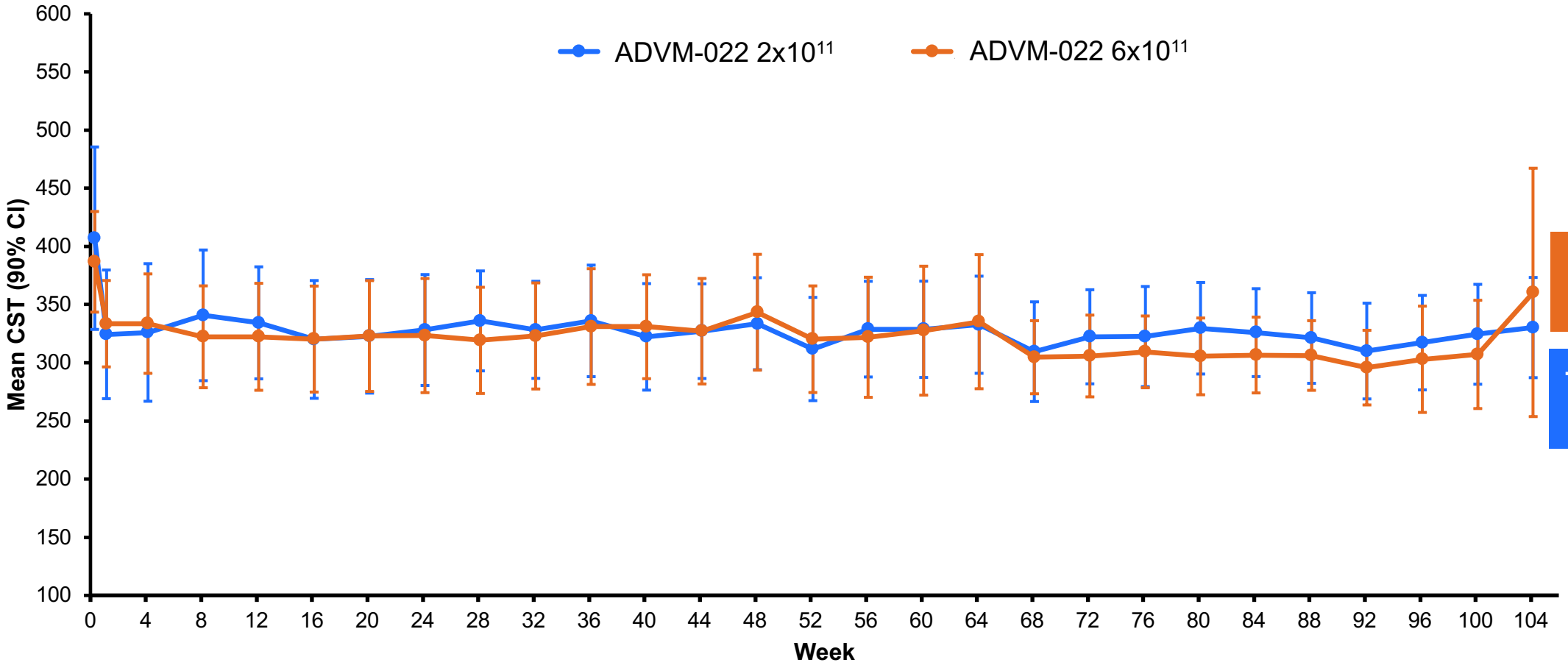
**+0.2 (-4.6, 5.0)**
**All $2x10^{11}$ vg/eye**

**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**

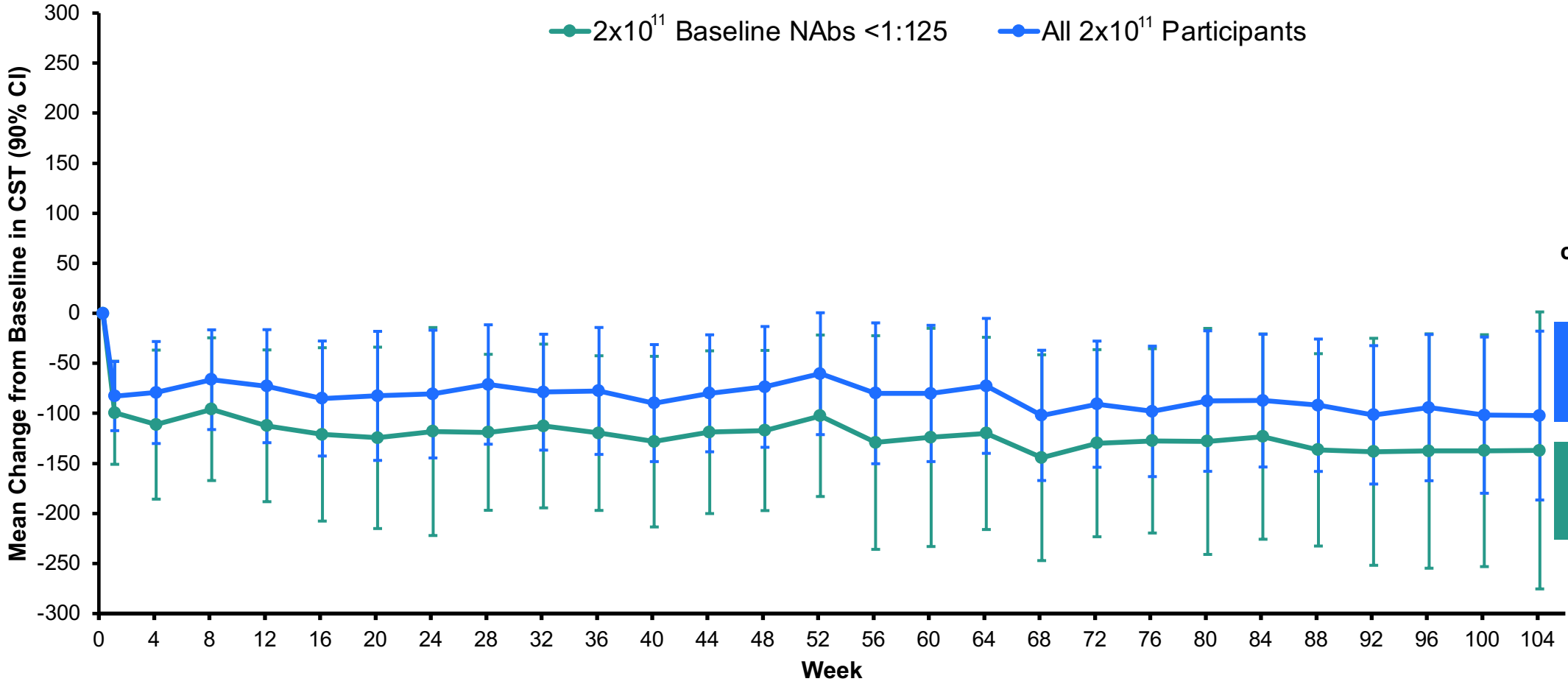
**-95.9 (-156.5, -35.3)**
**p = 0.015***
**2x10^11 vg/eye**

**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**

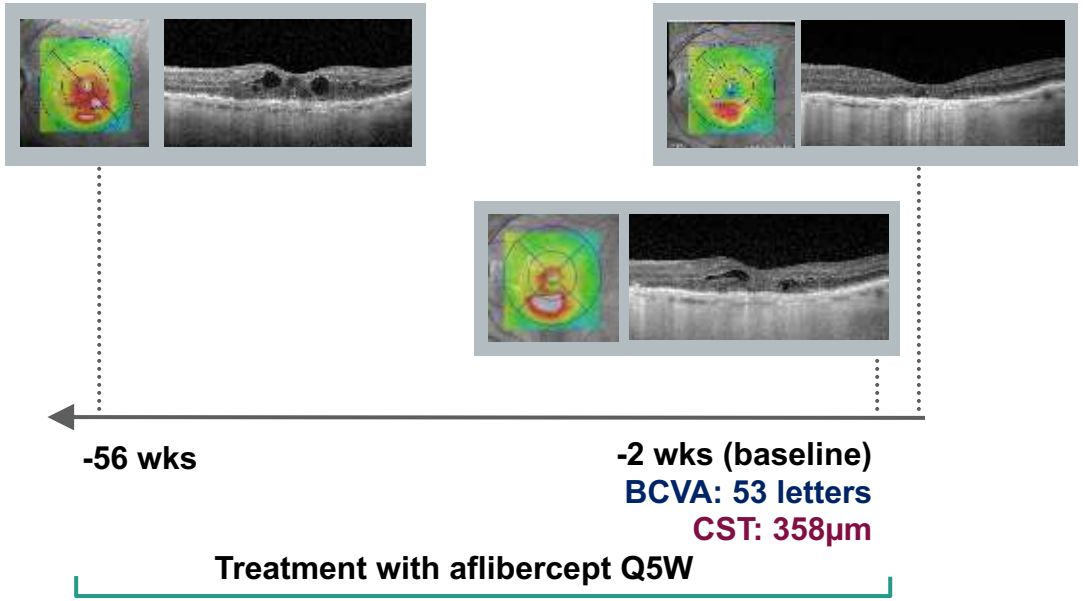
**-126.6 (-216.7, -36.5)**
**p=0.030***
**Baseline NAbs <1:125**

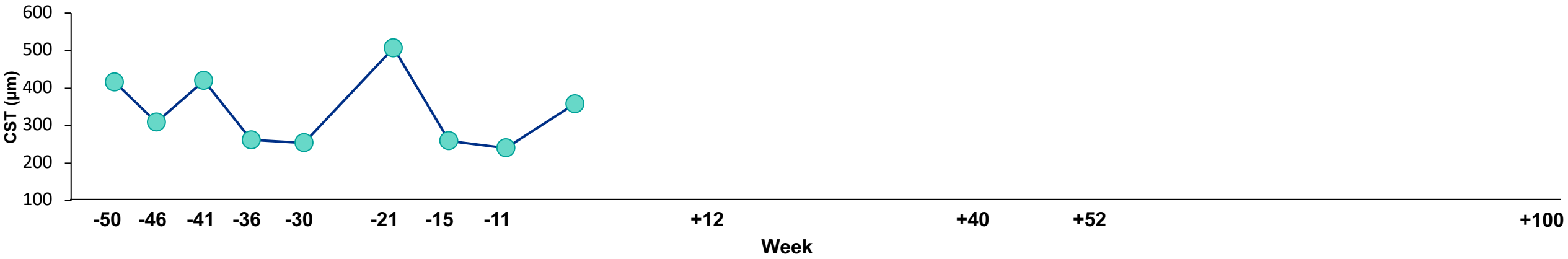
**Derived from a paired t-test comparing mean CST pre-ADVM-022 and at the last visit post-ADVM-022*

*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*

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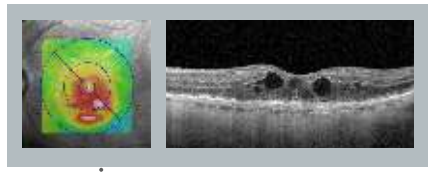
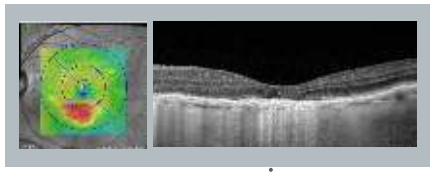
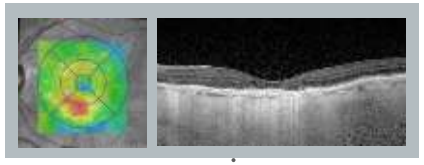
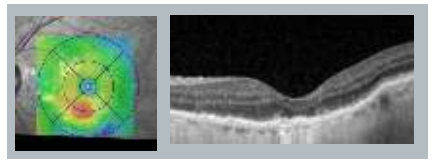
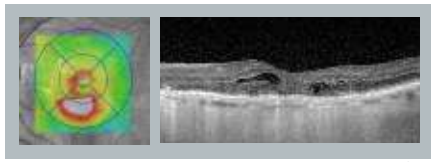
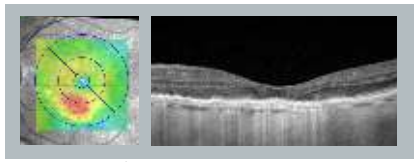
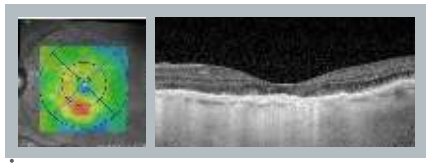








**-56 wks**

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

**Day 0**
**ADVM-022**

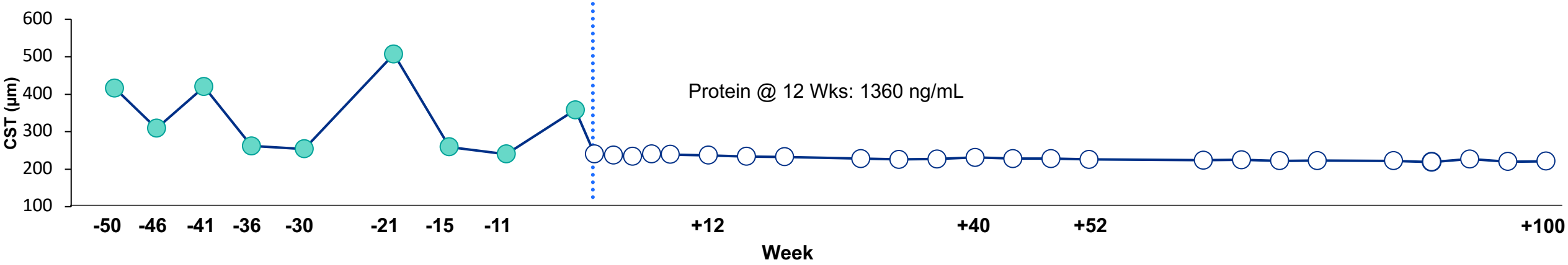
**+12 wks**
**BCVA: +13 letters**
**CST: -121µm**

**+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

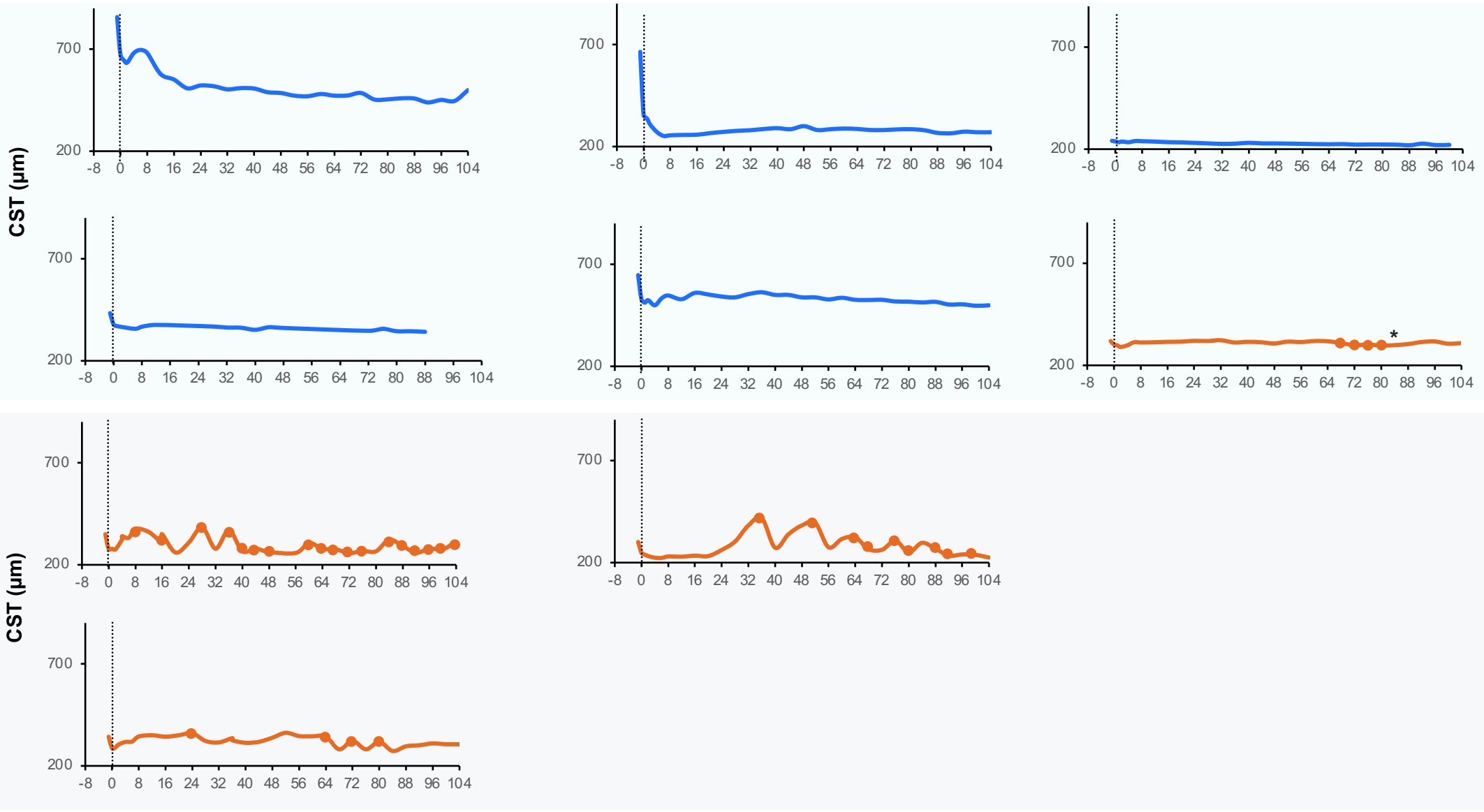
*No CST reading available at week 104. BCVA at week 104 was 58 letters

*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*

# Acknowledgements

## Investigators, Study Teams, and Participants

- David Boyer MD
- Brandon Busbee MD
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- John Han, PharmD
- Adam Turpcu, PhD