The OPTIC Study of Intravitreal Gene Therapy with ADVM-022 for Neovascular AMD (nAMD): The Role of Neutralizing Antibodies

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– On behalf of the OPTIC investigators –

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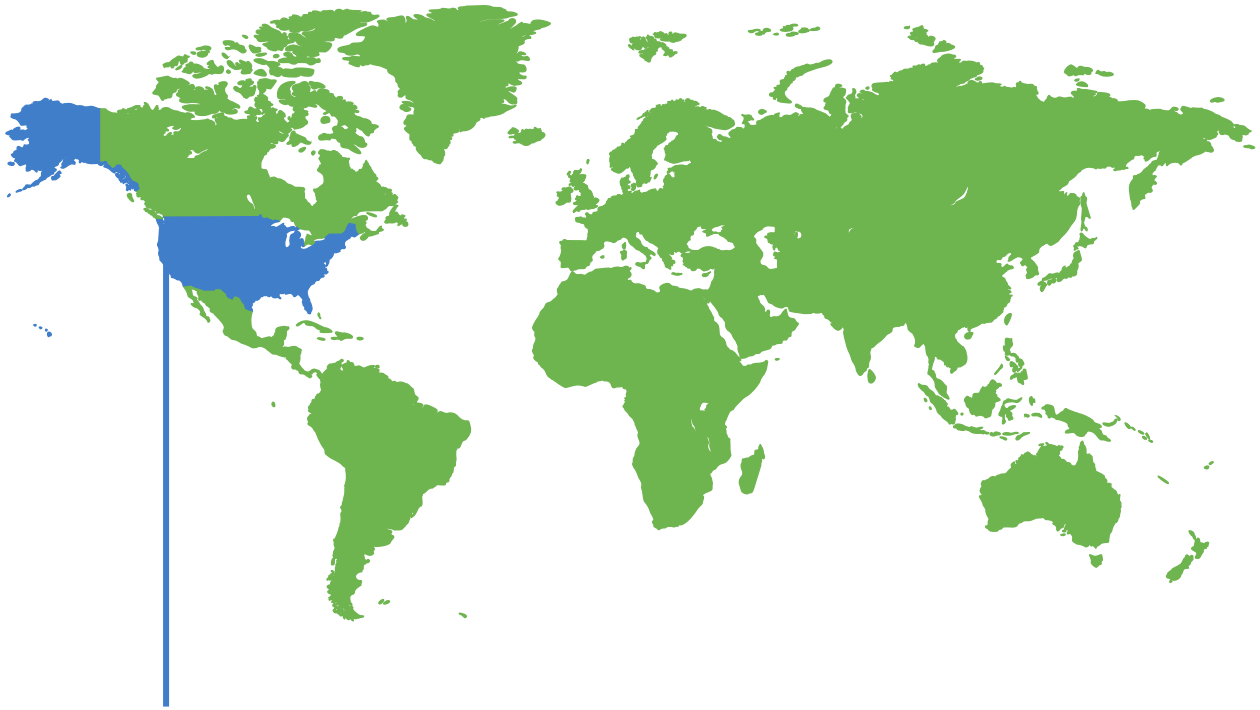
Disclosures

- 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

Wet AMD: Leading Cause of Blindness in Patients Over 65

20M people living with wet AMD Worldwide[1,2]



1.5M people impacted by wet AMD in the U.S.[1,2]

Real World Outcomes with Current Standard of Care are Suboptimal

Frequent anti-VEGF injections required leading to poor adherence

Lifetime need for frequent injections overburdens patients, caregivers, and healthcare providers

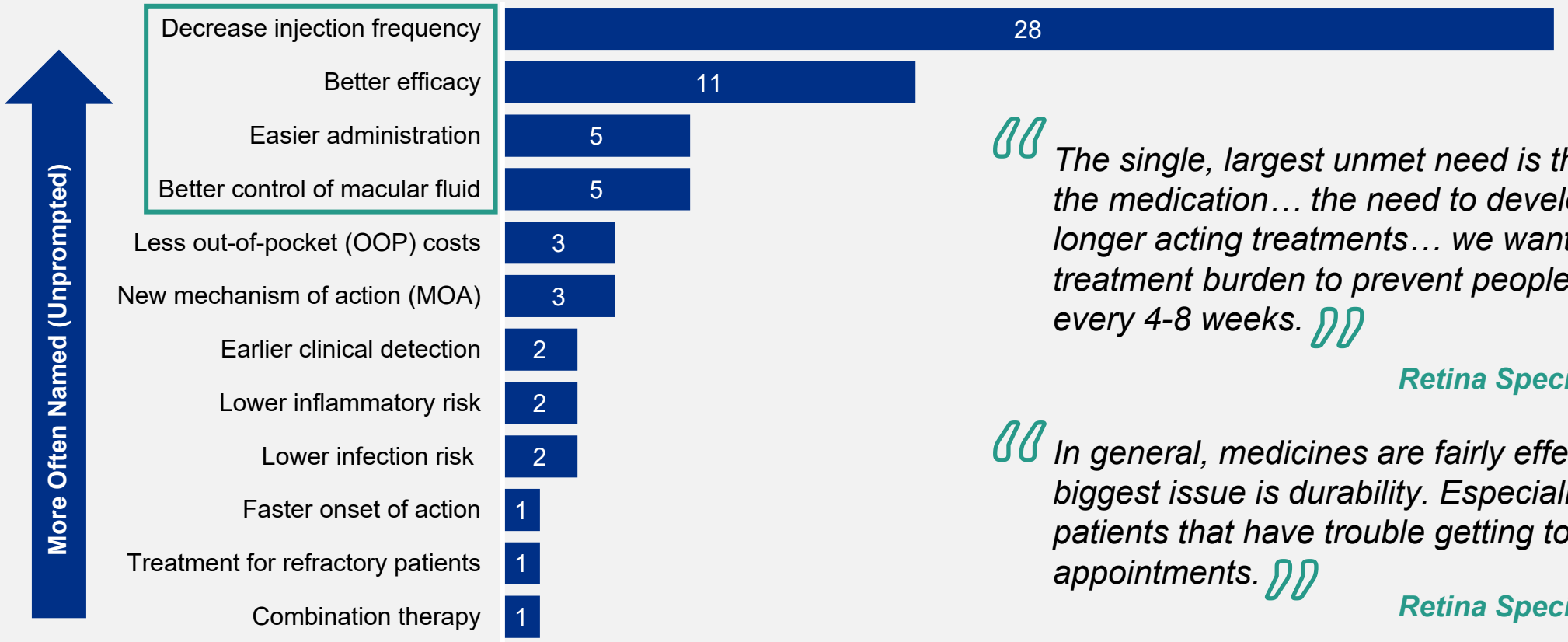
$139 billion in U.S. annual economic burden of vision loss, including falls, cognitive decline and depression*

[1]Bright Focus Foundation. Age-Related Macular Degeneration: Facts & Figures. [Internet; cited October 2021]. Available from: https://www.brightfocus.org/macular/article/age-related-macular-facts-figures. [2]Wong WL, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2:106–16.

Durable Treatment to Reduce Injection Frequency is the Largest Unmet Need

Largest Unmet Needs for Wet AMD Patients as Reported by Retina Specialists

(Number of mentions, N=30)



> *"The single, largest unmet need is the durability of the medication… the need to develop systems with longer acting treatments… we want to reduce the treatment burden to prevent people from coming in every 4-8 weeks."*
>
> ***Retina Specialist***

> *"In general, medicines are fairly effective… the biggest issue is durability. Especially for elderly patients that have trouble getting to appointments."*
>
> ***Retina Specialist***

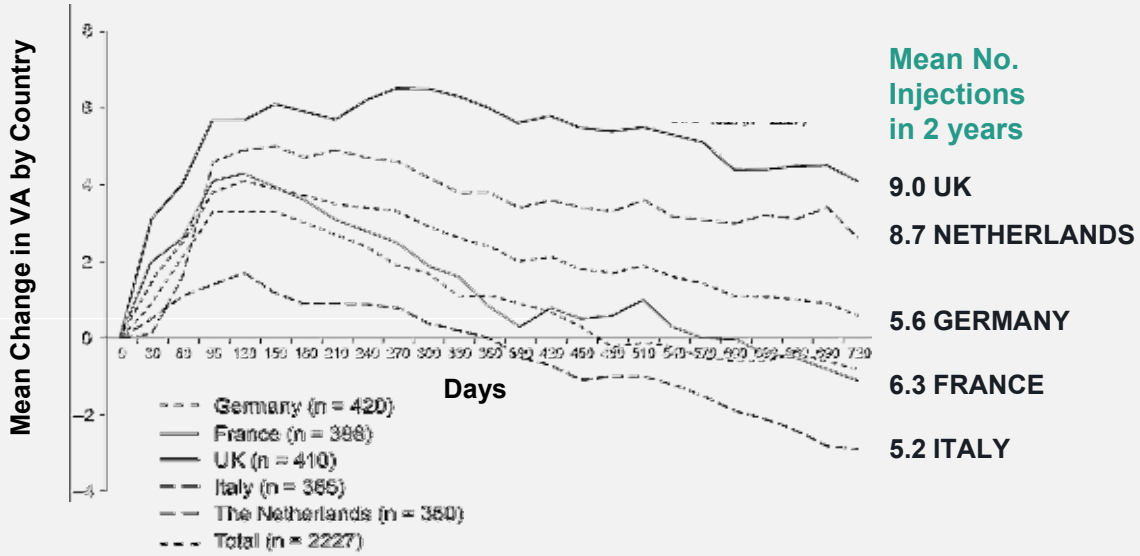
Source: ADVM Third-party Market Research; wet AMD (wet age-related macular degeneration); MOA, mode of action; OOP, out-of-pocket

Real-World Evidence Shows Reduction in Vision Over Time

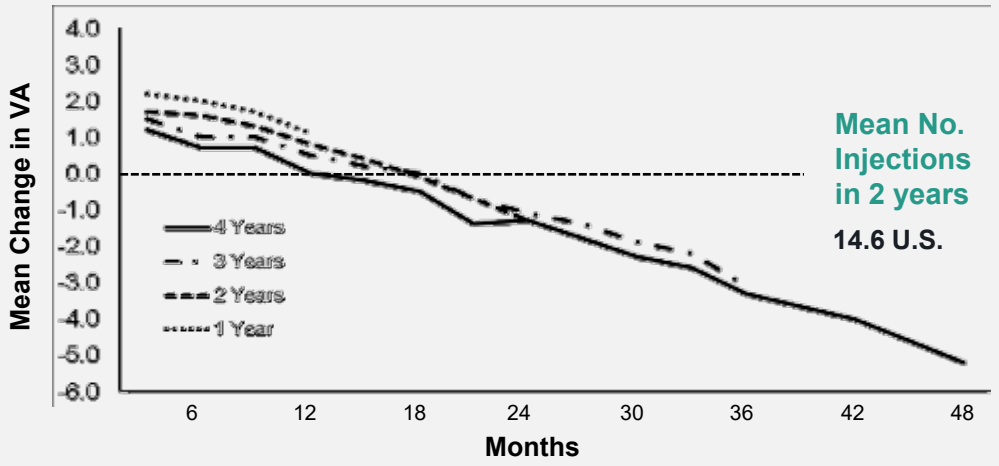
- Reduction in vision caused by poor adherence to frequent injection regime due to:
  - Insufficient treatment
  - Persistence of macular fluid between injections
- Bolus anti-VEGF injections result in fluctuations in macular fluid shown to have negative impact on vision over time

- Gene therapy administered as single, in-office IVT injection has potential to deliver:
  - Long-term efficacy
  - Reduced patient burden
  - Stabilization of macular fluid/reduced fluctuations
  - Potential to maintain or improve vision and anatomical outcomes in previously treated patients

EUROPE 2015 2-Year Study[1] (N = 2,227 patients)

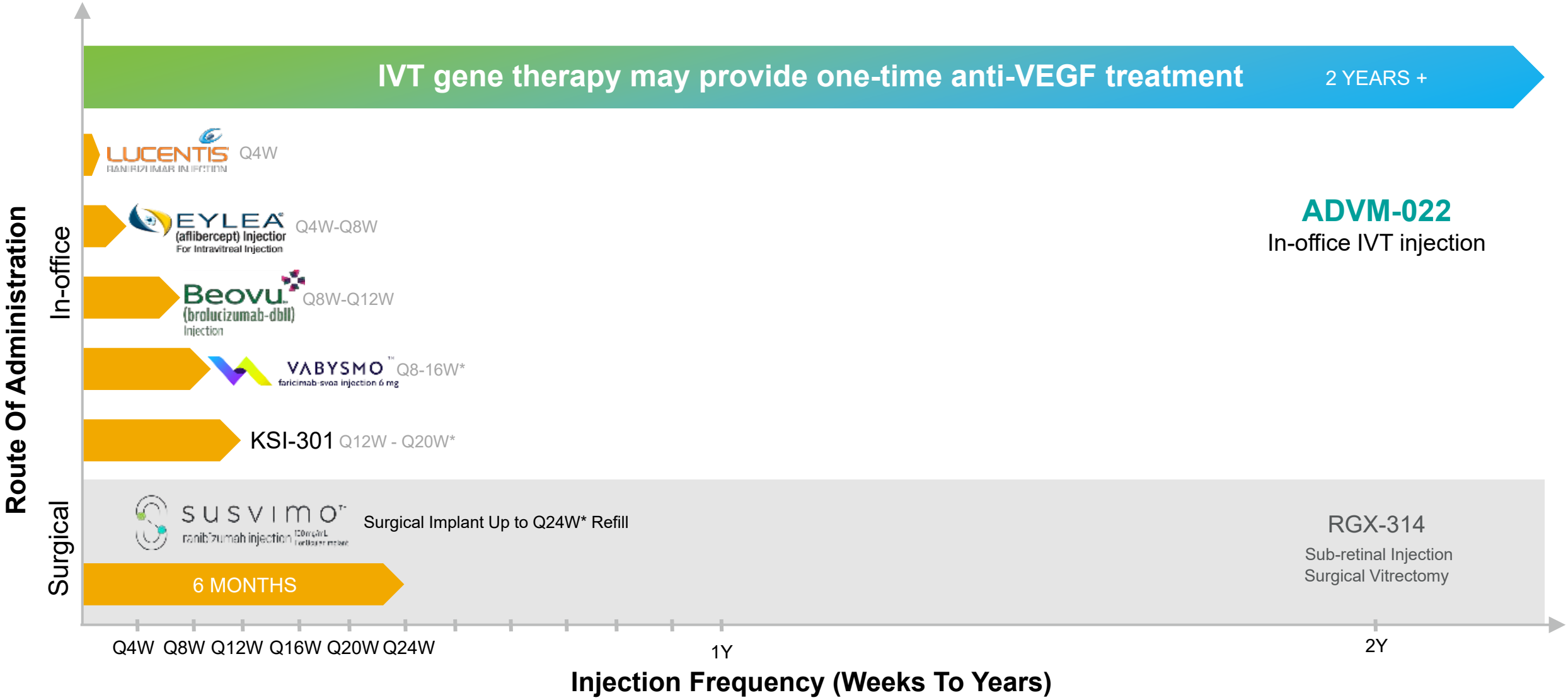


U.S. 2020 1-4 Year Study[2] (N = 79,885 patients)



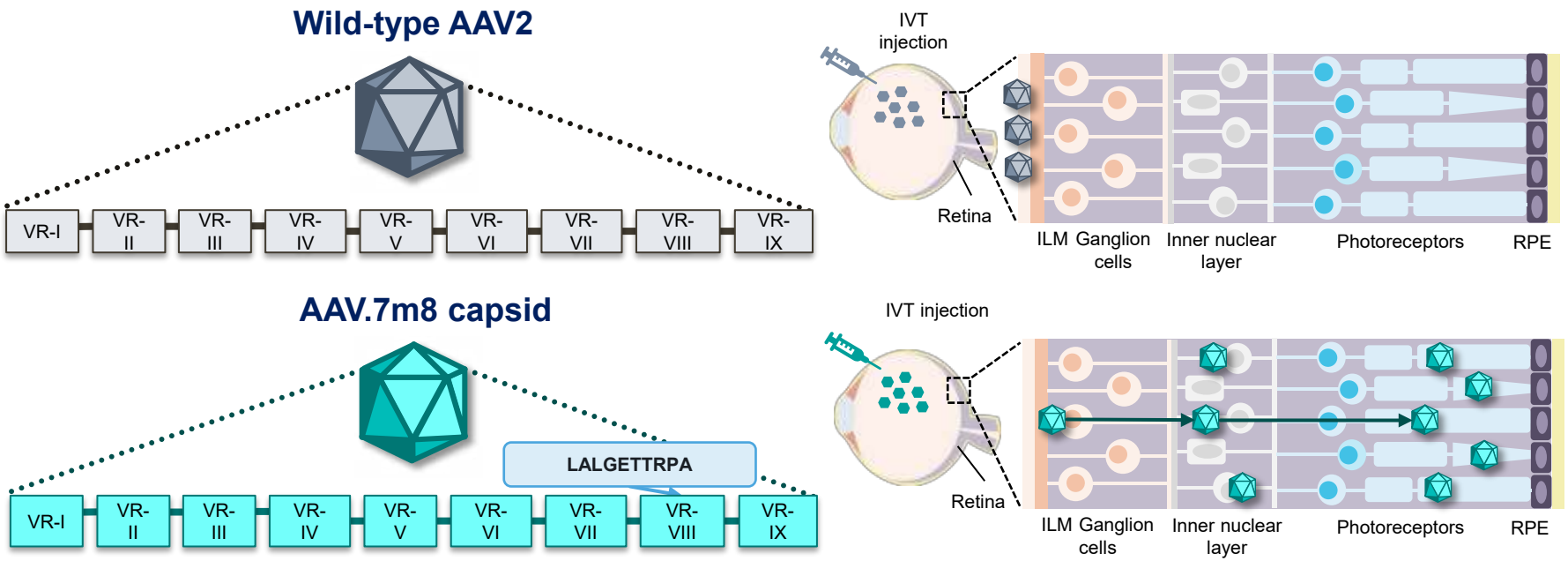
[1]The AURA Study, adapted from Holz FG et al. Br J Ophthalmol 2015; 99 (2): 220–226;
[2]Adapted from SIERRA-AMD, Khanani A, et al. Ophthal. Retina 2020 Feb; 4(2):122-123. EMR= Electronic Medical Records

Retina Landscape is Evolving - Gene Therapy Will Bring Significant Innovation as a Transformative Medicine

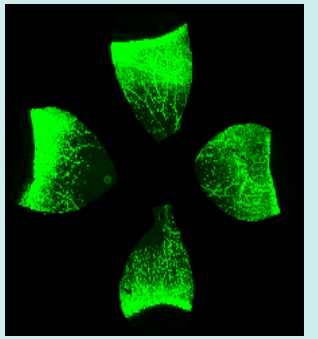


Timeline for illustrative purposes; *Note: based on wet AMD Phase 3 design

Proprietary AAV.7m8 Capsid Facilitates Efficient Retinal Transduction Enabling IVT Gene Therapy[1-4]



- Advanced AAV.7m8 vector developed using directed evolution to:[1]
  - Enable efficient intravitreal delivery
  - Increase transduction of retinal cells
  - Increase protein expression



Green fluorescent protein expression in non-human primate retina

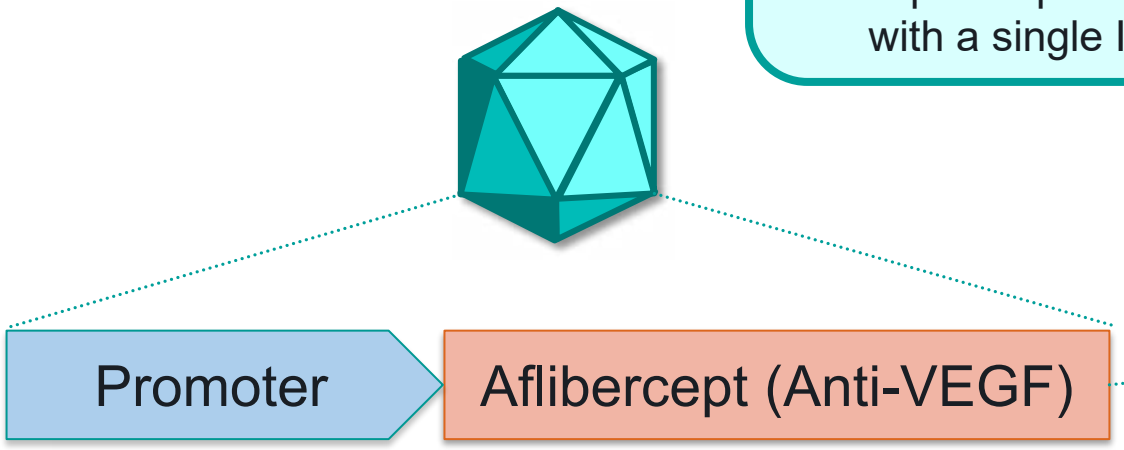
AAV, adeno-associated virus; ILM, inner limiting membrane; IVT, intravitreal; RPE, retinal pigment epithelium; VR, variable region.

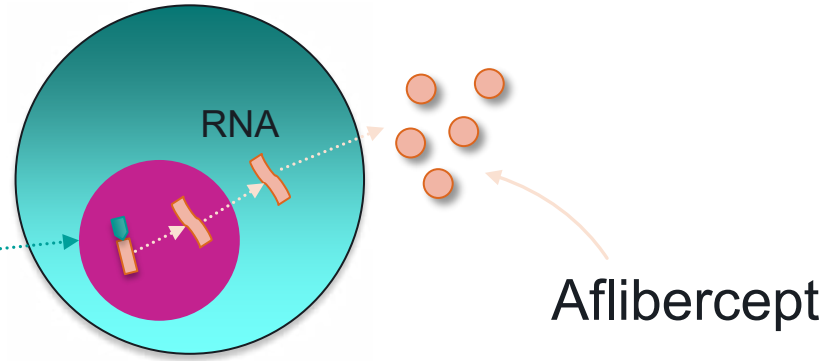
1. Grishanin, R et al. *Mol Ther.* 2019;27:118–129; 2. Bennett A, et al. *J Struct Biol*. 2020;209(2):107433; 3. Dalkara D, et al. *Sci Transl Med*. 2013;5(189):189ra76; 4. Khabou H, et al. *Biotechnol Bioeng*. 2016;113(12):2712-2724.

ADVM-022 Is a Novel Biofactory Approach to Gene Therapy Designed for Continuous Delivery of Aflibercept (Anti-VEGF) by Intravitreal Injection

ADVM-022 does not replace or modify an abnormal gene, but instead acts as a biofactory to continuously deliver anti-VEGF therapeutic protein to the retina with a single IVT injection

AAV.7m8 capsid





Aflibercept Expression Cassette

Target Retinal Cell Expresses Aflibercept

Strong, Ubiquitous Promoter Designed for Robust Protein Expression

Codon-Optimized cDNA

cDNA, complementary deoxyribonucleic acid; IVT, intravitreal; RNA, ribonucleic acid; VEGF, vascular endothelial growth factor.

Grishanin R, et al. *Mol Ther*. 2019;27:118-129.

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

Status

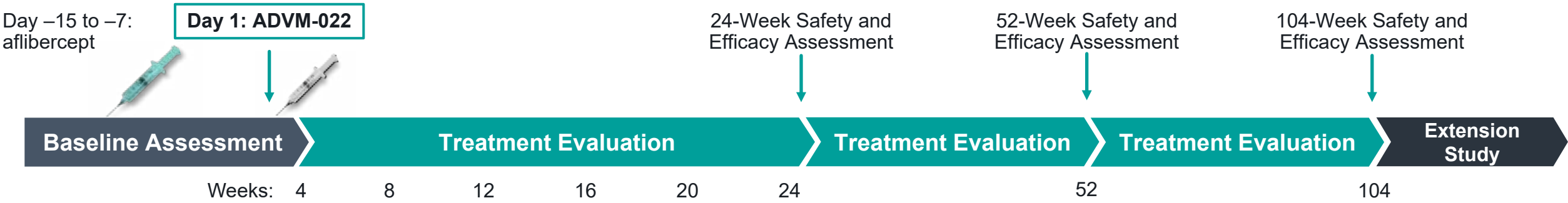
- 4 cohorts fully enrolled
- Follow-up to 104 weeks

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



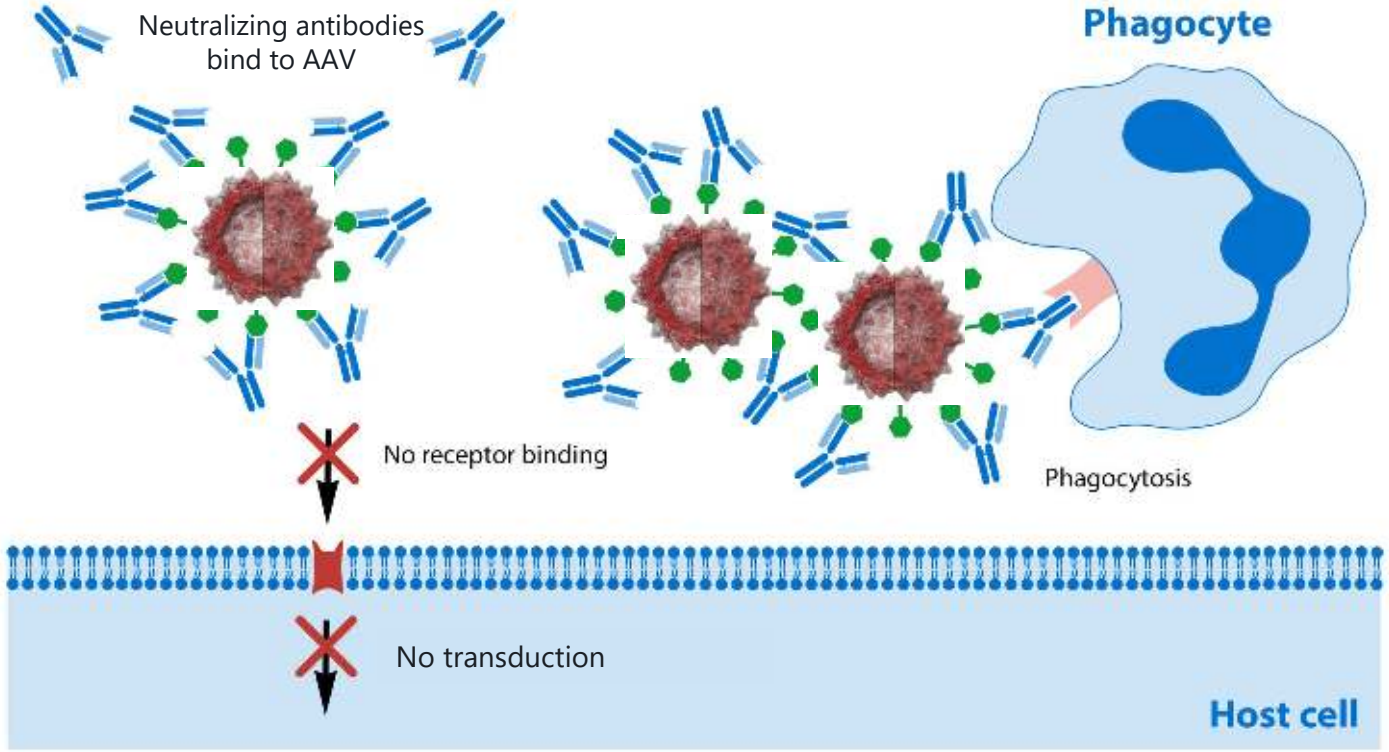
	Prophylaxctic Steroid Regimen
Cohort 1 (n=6) 6 x 10^{11} high dose	Oral*, 13d
Cohort 2 (n=6) 2 x 10^{11} low dose	Oral*, 13d
Cohort 3 (n=9) 2 x 10^{11} low dose	Eye Drops**, 6wks
Cohort 4 (n=9) 6 x 10^{11} high dose	Eye Drops**, 6wks

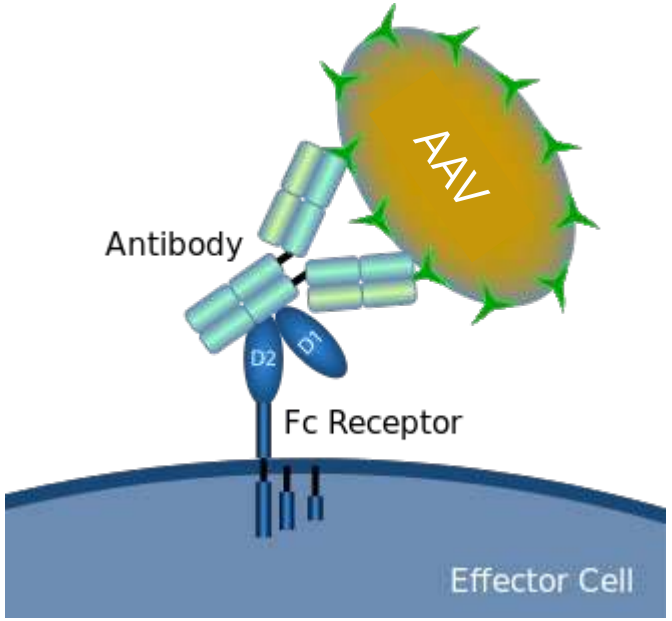
NAbs Analysis

- 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, 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; ETDRS, Early Treatment Diabetic Retinopathy Study; 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



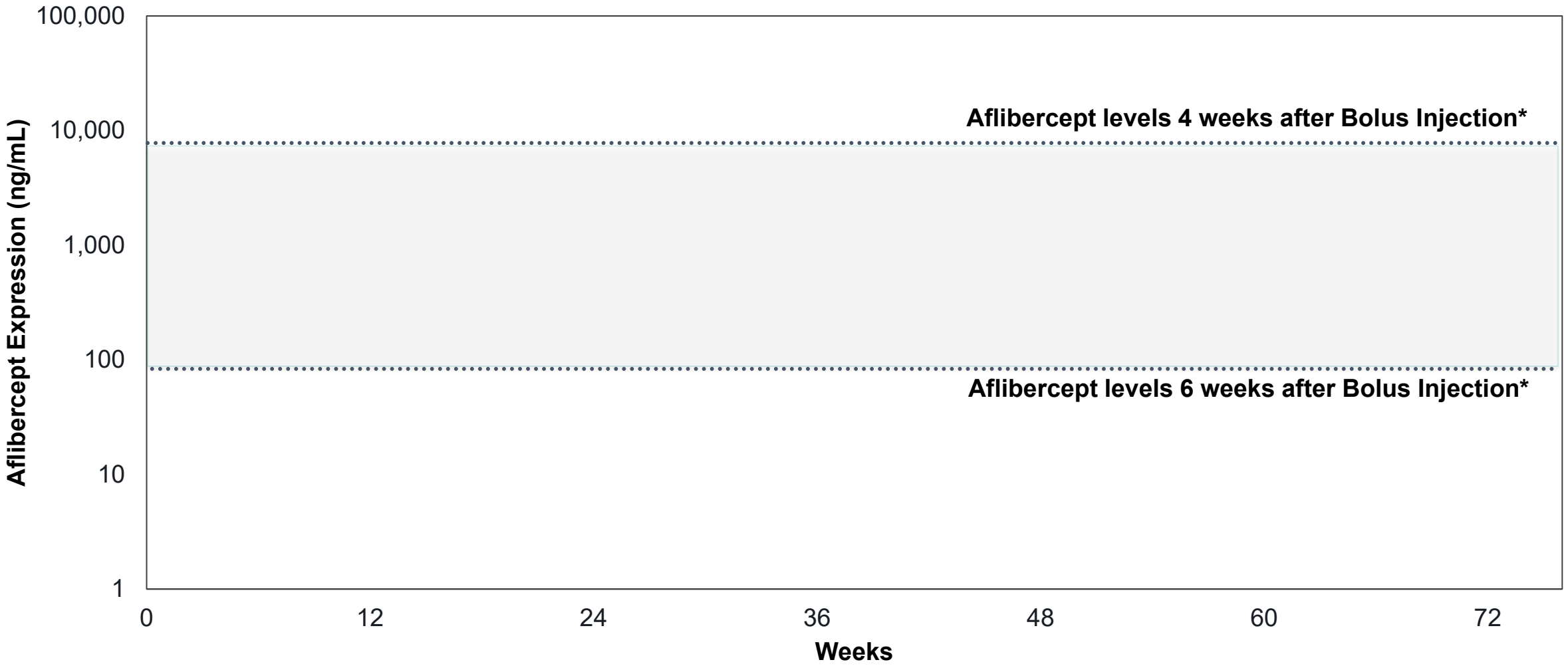


- The presence of NAbs can trigger the innate and adaptive immune system leading to AAV clearance and a reduction in transduction efficiency[1,2]

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.

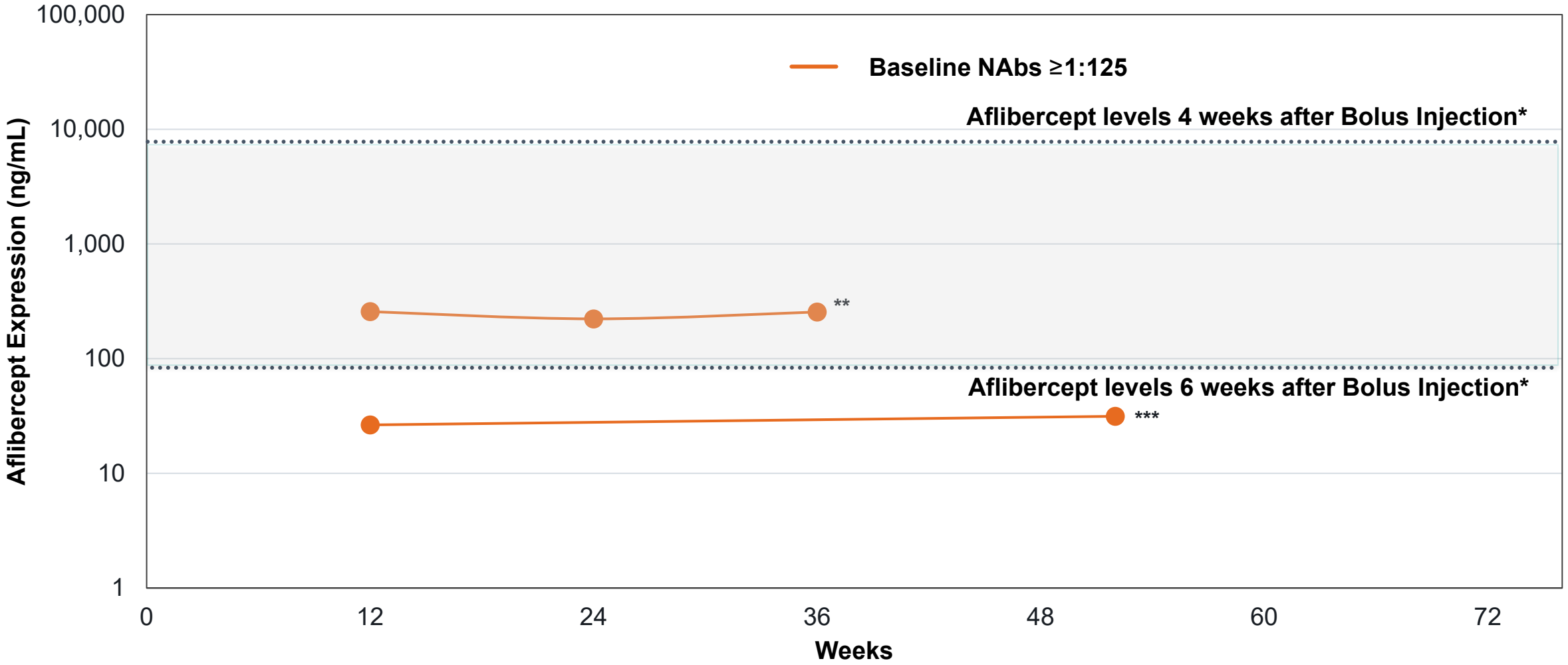
More Robust Aflibercept Protein Expression in Participants With Baseline NAb titers <1:125 at Among Participants Treated with ADVM-022 $2x10^{11}$ vg/eye



*Modeled based on Do DV, et al. *Retina.* 2020;40(4):643-647; ** Patient rescued at Week 36; *** Patient rescued at Week 24. Sample collected 28 weeks after supplemental injection. Protocol amendment for aqueous sample collection for patients who consented. No samples available from Cohort 2. To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.

Data cut: July 16, 2021

More Robust Aflibercept Protein Expression in Participants With Baseline NAb titers <1:125 at Among Participants Treated with ADVM-022 2x10^{11} vg/eye



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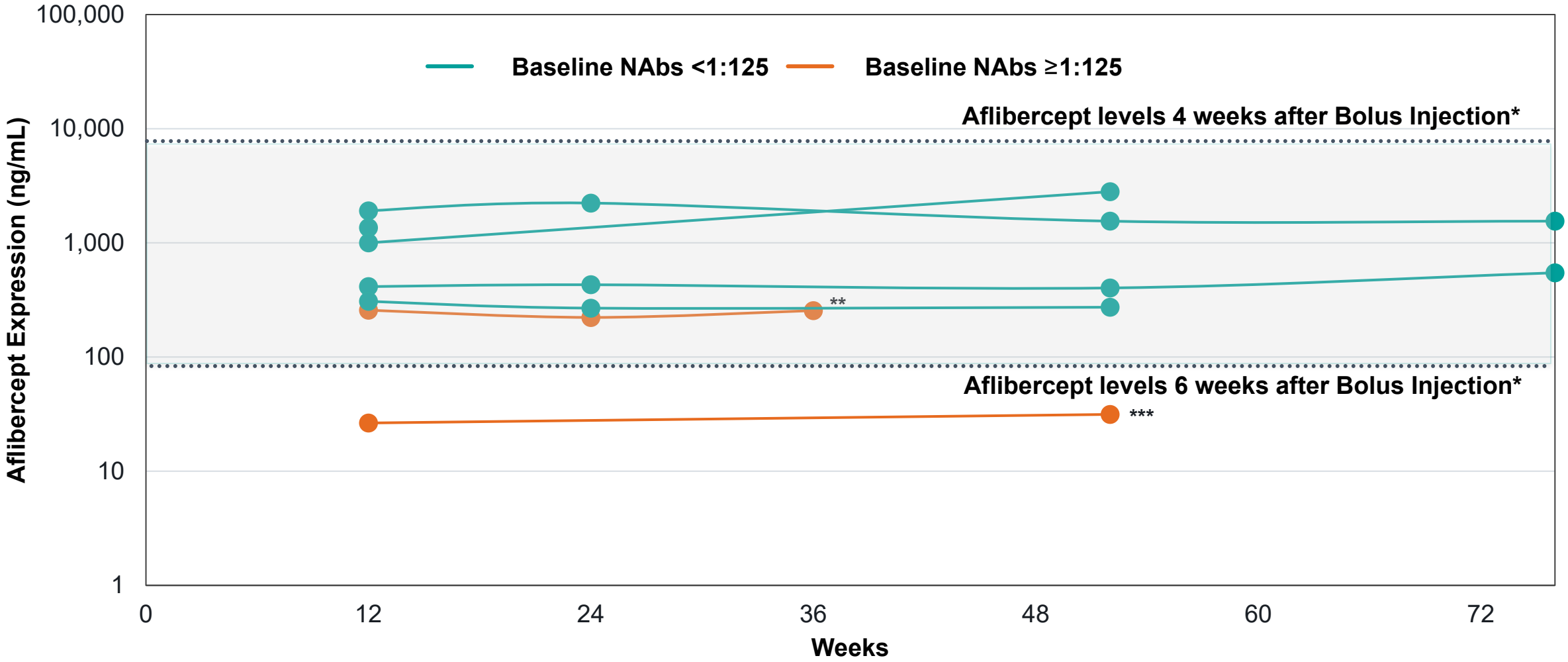

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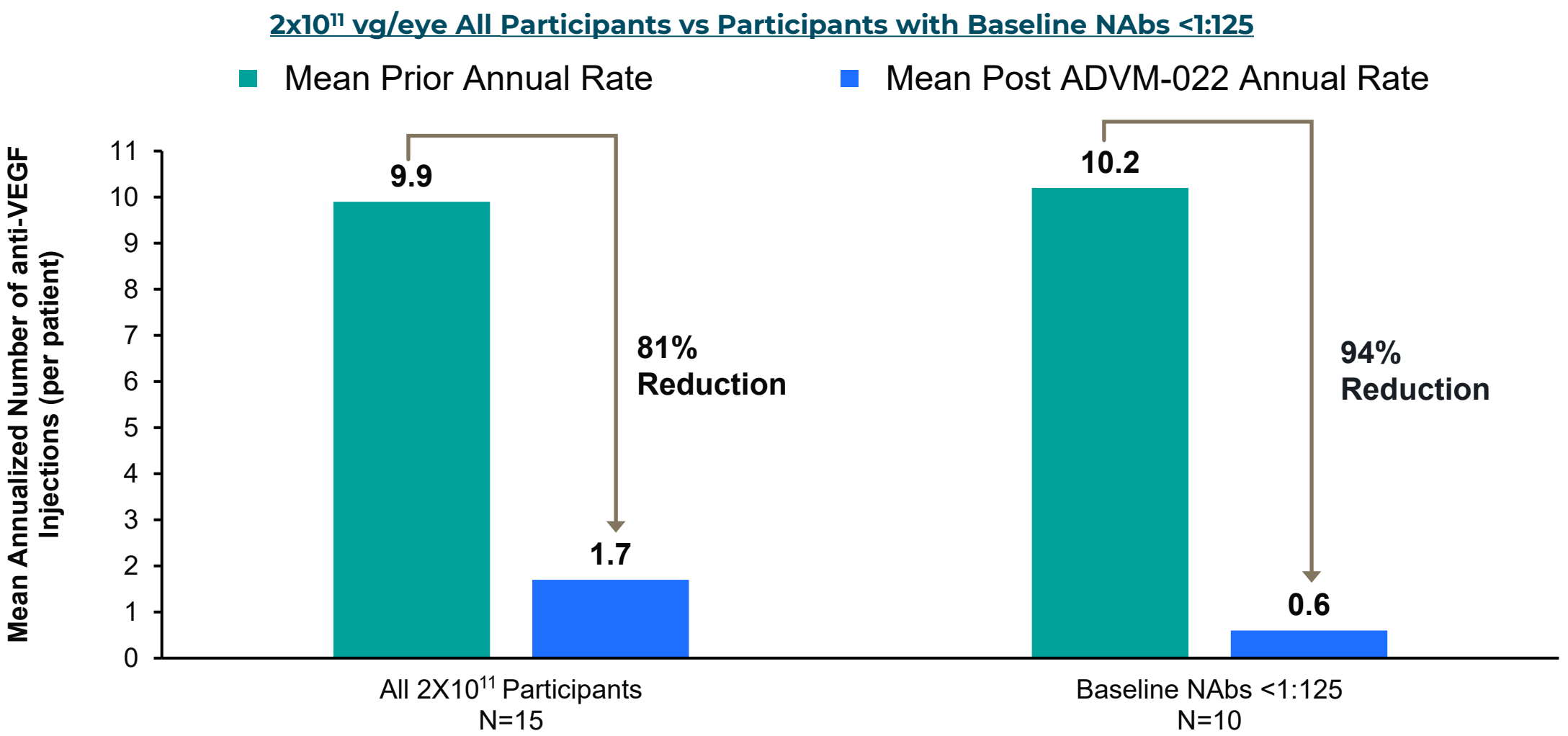
Data cut: July 16, 2021

94% Reduction in Annualized Anti-VEGF Injections in Participants With Baseline NAbs <1:125

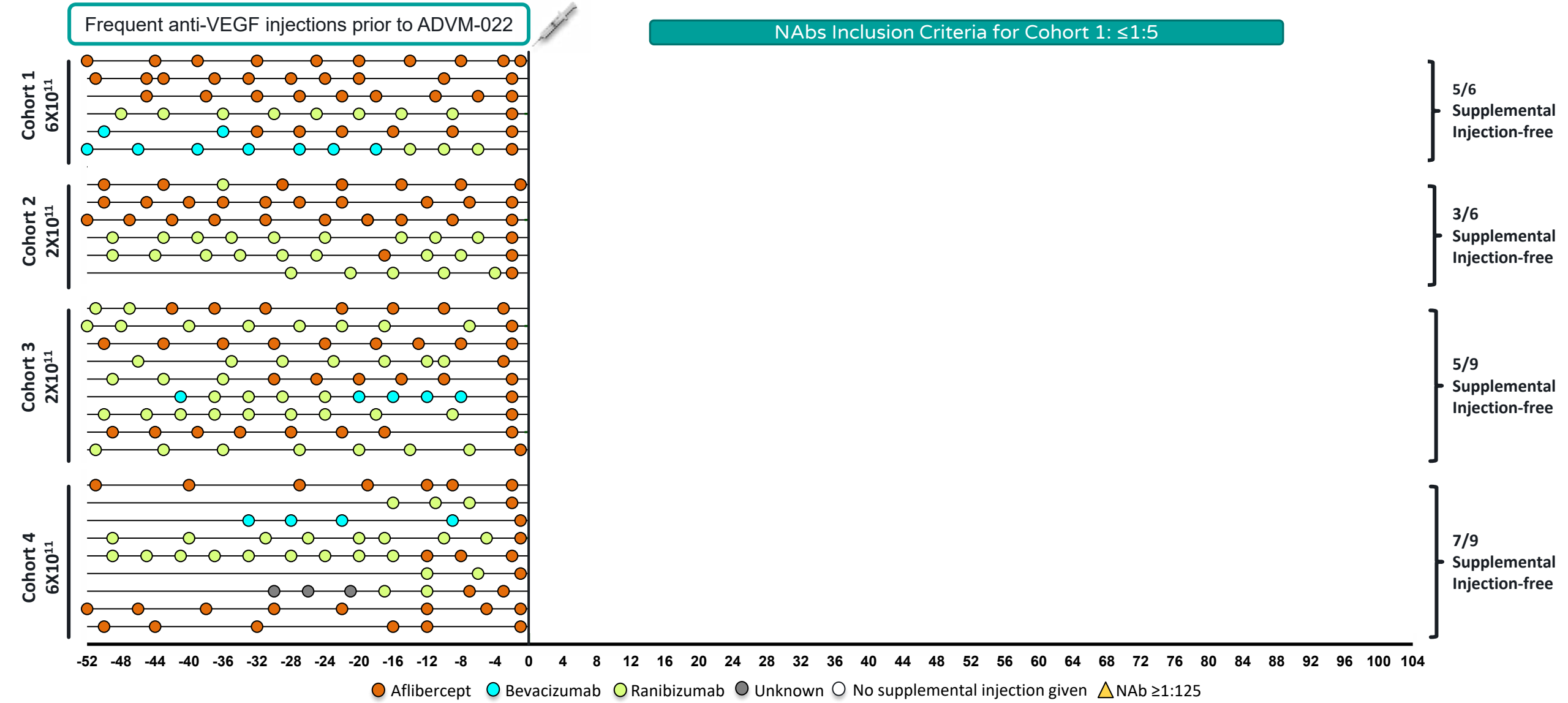


Annualized rate (Prior) = (number of IVTs in 12 months prior to ADVM-022) / (days from the first IVT in the past 12 months to ADVM-022 / 365.25).
Annualized rate (Post) = (numbers of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25).

A 97% reduction in annualized anti-VEGF Injections was observed in the 6x10[11] group.
NAb, neutralizing antibody; VEGF, vascular endothelial growth factor.

Data cut: July 16, 2021

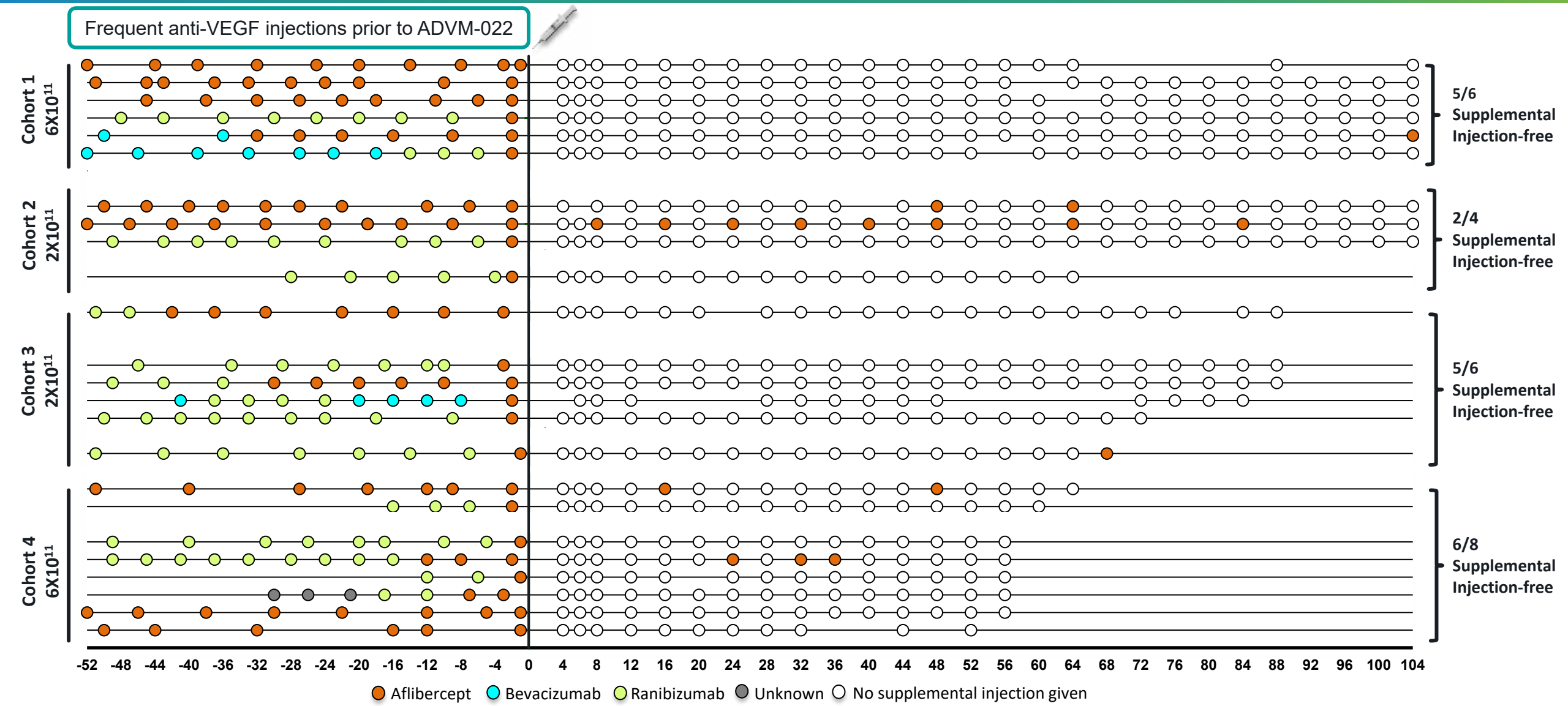
Reduction in Requirement for Supplemental Anti-VEGF Injections Following a Single IVT Injection of ADVM-022 in All Participants



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.

Data cut: July 16, 2021

Potential Impact of Baseline NAbs on Supplemental Aflibercept Injections: Exclude ≥ 1:125 NAbs



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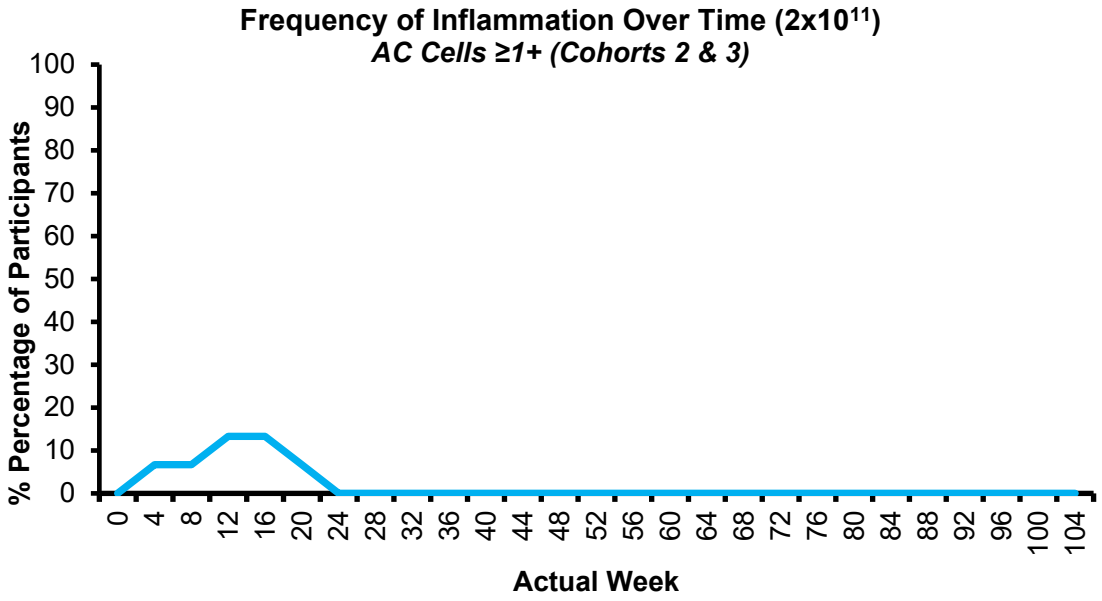
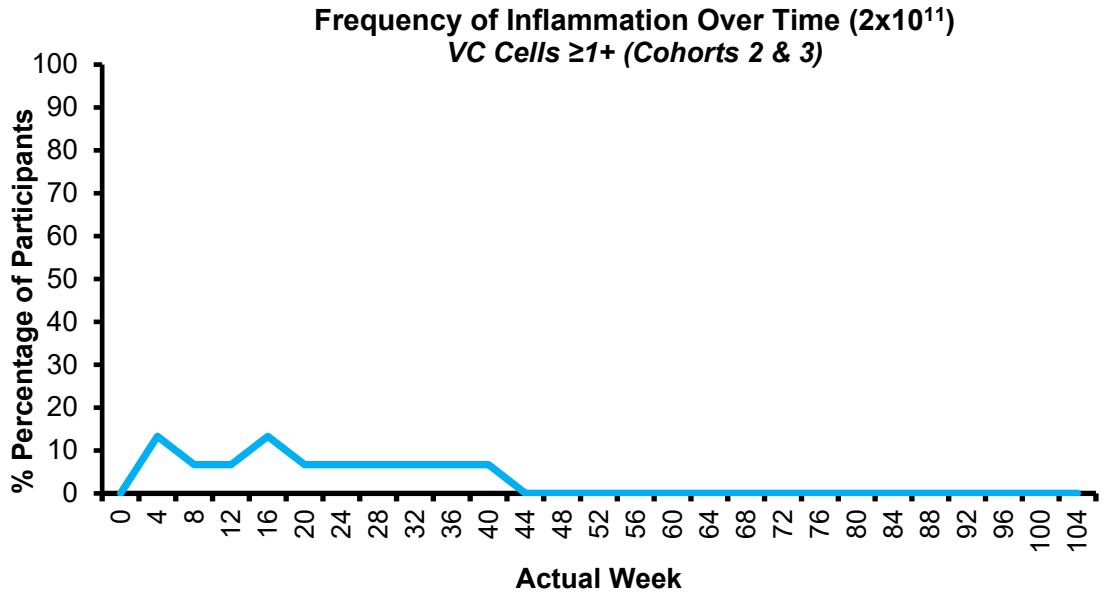
Data cut: July 16, 2021

Safety Summary

- ADVM-022 related events were mild (83%) or moderate (17%) across all cohorts
- One SAE of uveitis occurred in cohort 1 ($6x10^{11}$ dose) which was responsive to topical corticosteroids
- All inflammation observed at the $2x10^{11}$ dose was responsive to topical corticosteroids
  - At most recent follow-up, no patients in the $2x10^{11}$ vg/eye cohorts required any topical corticosteroids to treat inflammation
- No correlation between NAb titer and inflammation was observed
- ADVM-022 was well tolerated in the nAMD population studied in OPTIC

Frequency of Inflammation Decreases Over Time



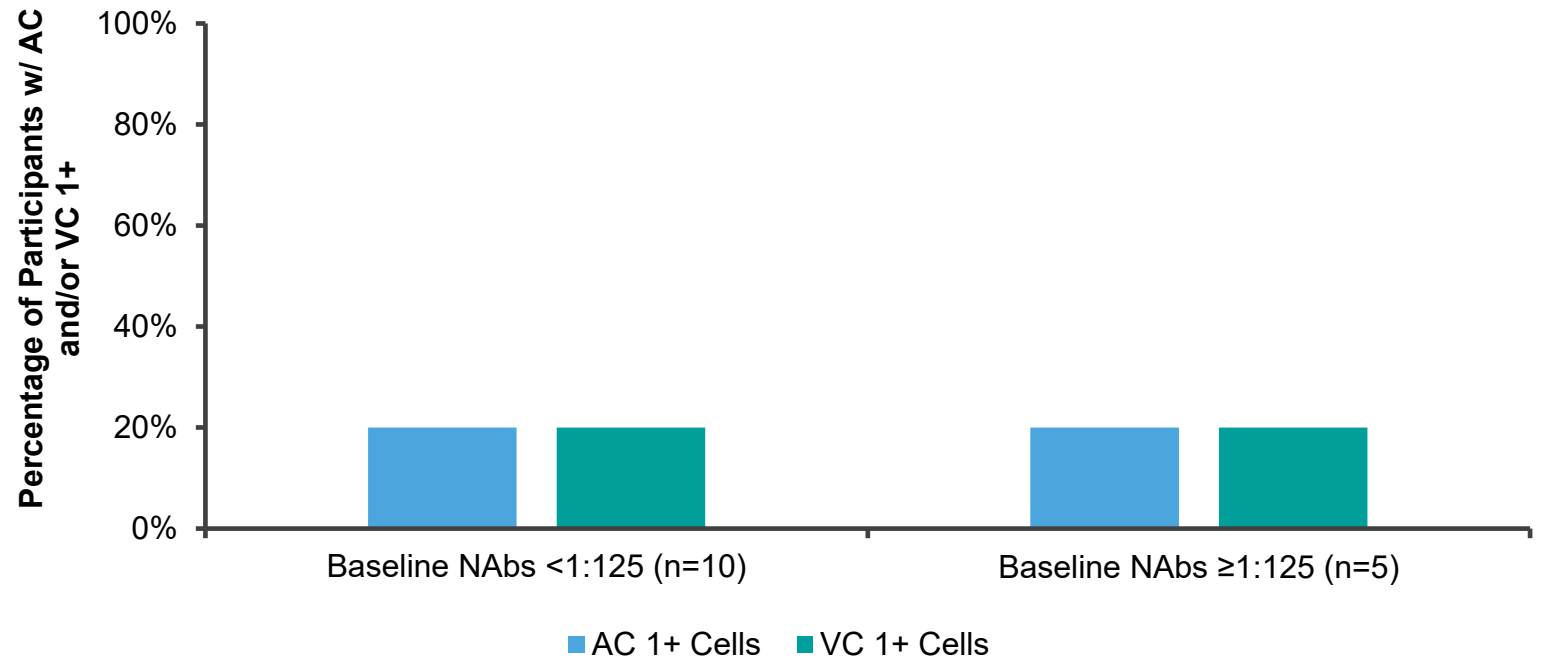


AC, aqueous cells; NAb, neutralizing antibody; nAMD, neovascular age-related macular degeneration; SAE, serious adverse event; VC, vitreous cells.

No Correlation Was Observed Between Baseline NAbs and AC and/or VC Inflammation

- No correlation between baseline NAbs and safety events was observed. Additionally, baseline NAbs were not associated with occurrence or duration of inflammation.
- AC inflammation does not seem to correlate with NAbs at screening or when there is a fluctuation on-study
- VC inflammation does not seem to correlate with NAbs at screening or when there is a fluctuation on-study
  - A patient in Cohort 2 with VC 3+ at the beginning of the study did not take oral prednisone

Percentage of Participants on $2x10^{11}$ vg/eye dose with 1+ AC and/or VC at Any Study Visit (n=15)



AC, aqueous cells; NAb, neutralizing antibody; VC, vitreous cells.

Conclusions

- The mean annualized anti-VEGF injection rate was reduced by 81% in all participants receiving $2x10^{11}$ vg/eye ADVM-022 and 94% in participants with NAbs titers <1:125
- Participants with baseline NAbs to AAV.7m8 <1:125 were more likely to demonstrate robust aflibercept protein expression and less likely to require supplemental anti-VEGF injections
- Both doses of ADVM-022 were well tolerated, with the $2x10^{11}$ vg/eye dose requiring less topical corticosteroid therapy to alleviate inflammation
    - At the most recent follow-up, no participants in the $2x10^{11}$ vg/eye dose group required any topical corticosteroids to treat inflammation
- Baseline NAbs were not associated with occurrence or duration of inflammation or other safety events
- A Phase 2 study in nAMD investigating the $2x10^{11}$ vg/eye dose and a lower $6x10^{10}$ vg/eye dose of ADVM-022 as well as new enhanced prophylactic steroid regimens, which are expected to include local steroids and a combination of local and systemic steroids, is planned
    - The first patient dosed in the Phase 2 study is expected in the third quarter of 2022

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Thank you!