IXO-VEC
IVT Gene Therapy for nAMD

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Adverum Corporate Overview (NASDAQ:ADVM)

$203.3 million

as of September 30, 2022

Funded into 2025

OPTIC 2 year data

20 million

people affected with wet AMD worldwide[1,2]

PIONEERING IVT GENE THERAPY

- Establishing intravitreal (IVT) gene therapy with 7m8 as the gold standard vector platform delivered in office in prevalent and rare ocular diseases*

BEST-IN-CLASS - ≥ 3 YEAR DURABILITY

- Proven AAV2.7m8 proprietary capsid delivering long-term therapeutic levels of anti-VEGF with Ixo-vec
- Dramatic reduction in treatment burden recognized with PRIME designation

>50% RESCUE FREE 2 YEAR after IXO-VEC 2e11vg/eye

- OPTIC - therapeutic aflibercept levels at week 10 predict long-term delivery, preserving or improving vision and CST fluctuations
- >80% reduction in annualized anti-VEGF at 2 years
- Phase 2 LUNA in wet AMD ongoing in US and planned in EU

[1]Bright Focus Foundation. Age-Related Macular Degeneration: Facts & Figures. Gensight GS030

[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.

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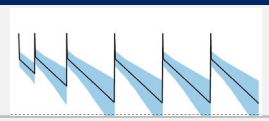
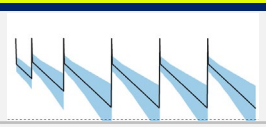
Retina Landscape in Wet AMD - Extending Treatment Benefit from Weeks to Years

	Aflibercept[1]	Faricimab[2]	RGX-314 (SR)[3] 6E10 & 1.6E11	RGX-314 (SCS)[4] 2.5E11, 5E11, and 1E12	Ixo-vec 2E11 (Ph2 Doses: 6E10 & 2E11)
PK				N/A	
Stable & Durable Anti-VEGF Levels	–	–	+	+	Sustained > 3 years
Simple IVT Injection	+	+	–	–	+
Potential "One-and-Done"	–	–	+	+	+
Treatment Duration	4-12 weeks	4-16 weeks	>3+ Years	6 Months	>3+ Years
Injection Free	–	–	17-50%	29-67%	53%
Reduction in Annualized anti-VEGF injections	–	–	58-67%	64-85%	81-93%
BCVA Maintenance/Gain 2 years (One Injection)	–	–	+	N/A	+
CST Maintenance/Reduction (One Injection)	–	–	+	N/A	+
Safety: No Inflammation (2 years)	N/A	N/A	+	N/A	+
Safety: No Hypotony (2 years)	N/A	N/A	+	N/A	+

1. Heier, et al. Ophthalmol. 2012;119(12), 2537-2548; 2. Khanani, et al. Ophthalmology Science. 2021;1(4),100076; 3. Gene Therapy for Neovascular AMD: Subretinal RGX-314: Phase I/IIa Long-Term Follow-Up Results up Results up to 4 Years. The American Academy of Ophthalmology 2022; 4. https://regenxbio.com/wp-content/uploads/2022/10/AAVIATE-10.3.2022_Final-for-Website.pdf, Accessed on November 16, 2022

Ixo-vec (ADVM-022)

IVT Gene Therapy for the Treatment of wet AMD

ADVM-022 Intravitreal Gene Therapy for Neovascular Age-related Macular Degeneration: End of Study Results from the 2-Year OPTIC Trial

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OPTIC: 2-Year Study Evaluating Ixo-vec in nAMD Patients Requiring Frequent Injections

OPTIC
Gene Therapy in nAMD

Primary Objective

- Safety and tolerability of ADVM-022 IVT injection

Secondary Objective

- Vision maintenance (BCVA)
- Anatomy (SD-OCT) change
- Need for supplemental therapy

Day –15 to –7: aflibercept

Day 1: ADVM-022

24-Week Safety and Efficacy Assessment

52-Week Safety and Efficacy Assessment

104-Week Safety and Efficacy Assessment

Baseline Assessment → **Treatment Evaluation** → **Treatment Evaluation** → **Treatment Evaluation** → **Extension Study**

3 years

Prophylaxis 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**, 6 wks
Cohort 4 (n=9) 6 x 10^{11} high dose	Eye Drops**, 6 wks

Supplemental Aflibercept (2 mg IVT) Criteria:

1. Loss of ≥10 letters in BCVA (ETDRS) from baseline that is attributed to intraretinal or subretinal fluid observed by the investigator
2. Increase in central subfield thickness >75 µm from baseline
3. Presence of vision-threatening hemorrhage due to AMD

Neutralizing Antibodies (NAbs) to AAV.7m8

- NAbs exclusion of >1:5 cohort 1 and >1:125 cohorts 2-4.
- 16% of screened patients excluded based on NAbs
- Baseline NAbs impact on treatment burden, aflibercept expression levels and safety was evaluated

Final 2-Year Analysis
**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.*
Final analysis includes all participants regardless of baseline neutralizing antibody titer.
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; QID, four times daily; SD-OCT, spectral domain optical coherence tomography; NCT03748784.

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ADVM-022 OPTIC Study Baseline Characteristics

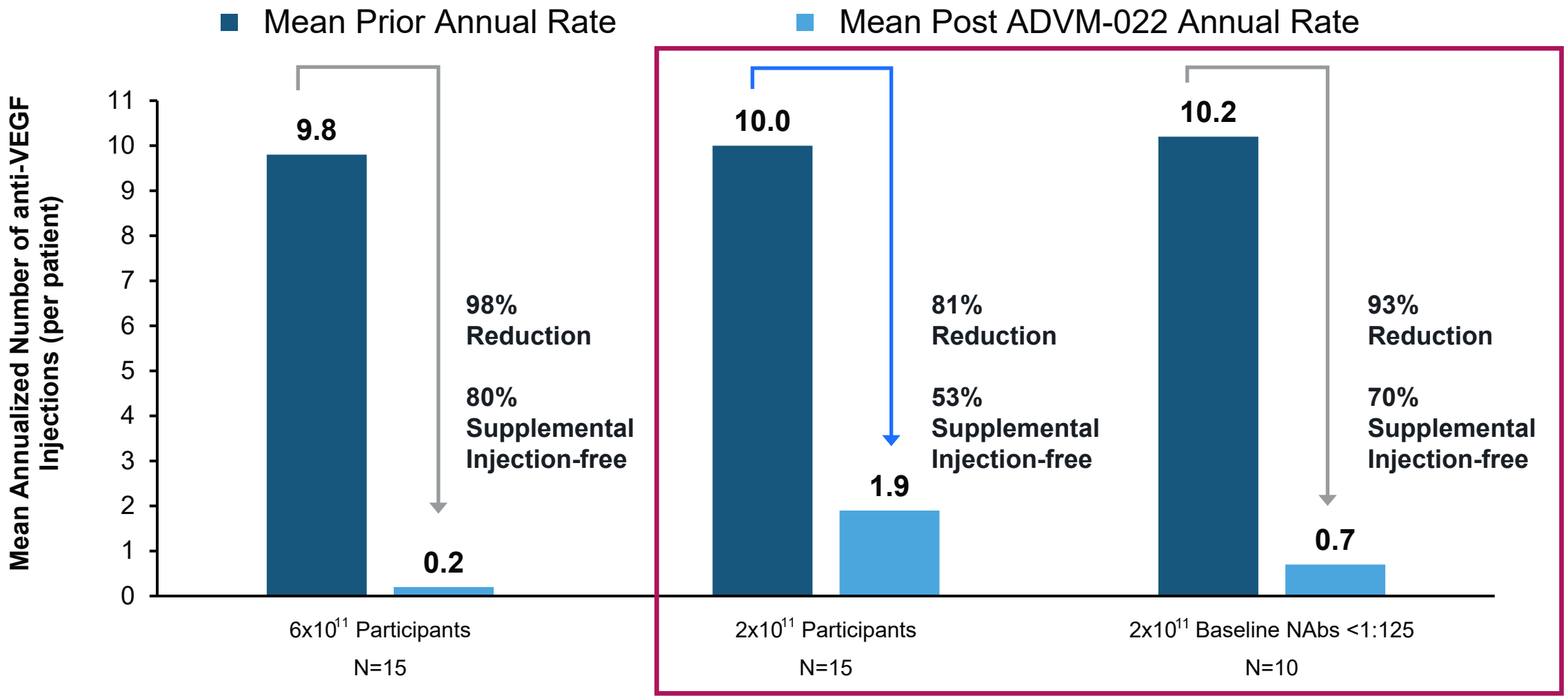
OPTIC Gene Therapy in nAMD

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)

**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

Final 2-Year Analysis

81-93% Reduction in Annualized Anti-VEGF After ADVM-022 IVT Injection at 2e11vg/eye and 53-70% Injection Free

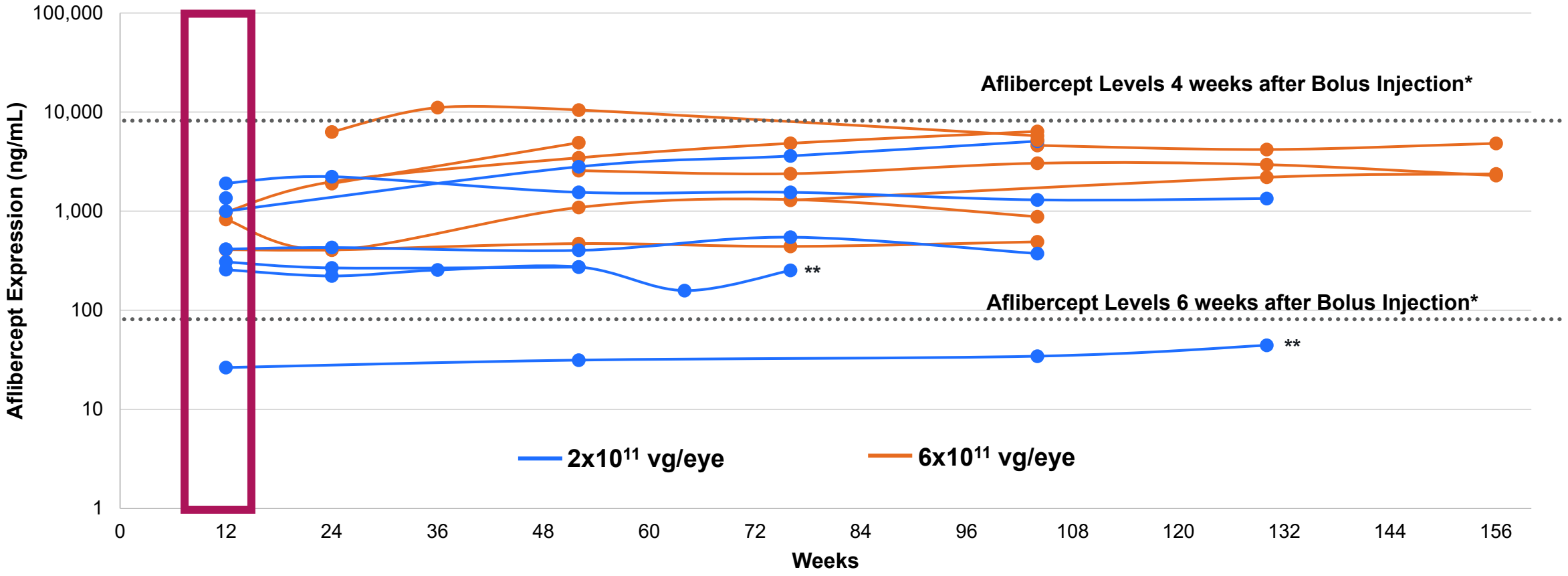


Data Cut: Feb 24, 2022. Annualized rate (Prior) = (number of IVTs in 12 months prior to ADVM-022) / (days from the first IVT in the past 12 months to ADVM-022 / 365.25). Annualized rate (Post) = (numbers of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25). NAbs, neutralizing antibodies; VEGF, vascular endothelial growth factor.

Therapeutic Aflibercept Levels Sustained Through 3 Years

OPTIC Gene Therapy in nAMD

Aflibercept levels at 10 weeks are predictive of long-term protein expression



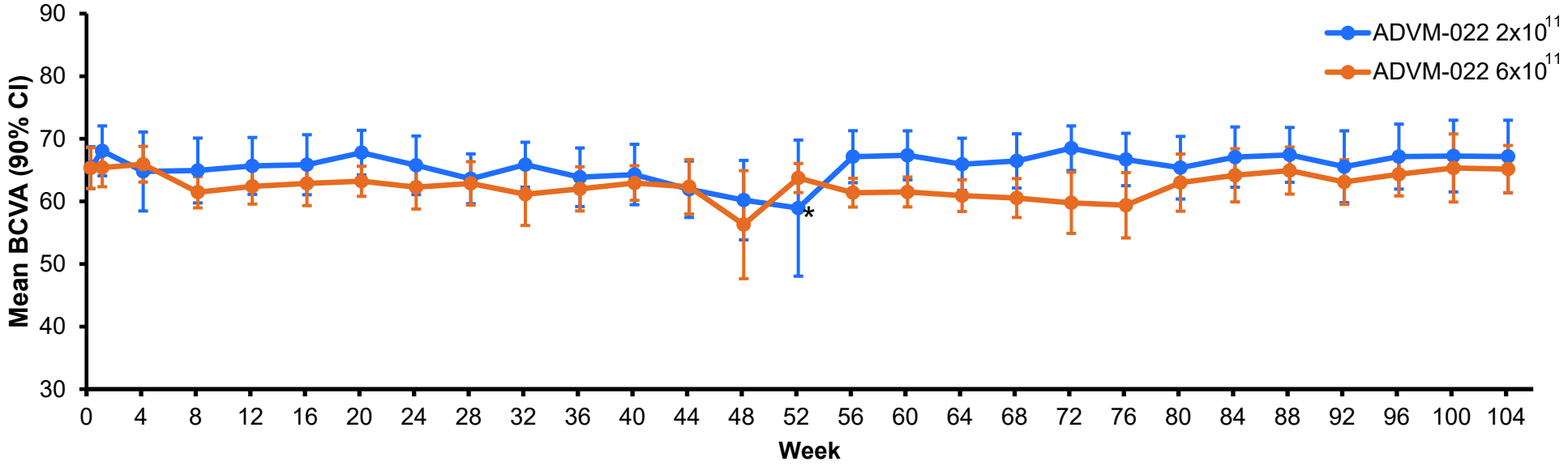
*Final 2-Year Analysis 2022. *Modeled based on Do et al. Retina 2020; 40:643-647. ** Participant received supplemental aflibercept injections Protocol amendment for aqueous sample collection for participants that consented. To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.*

ADVERUM Final 2-Year Analysis

ADVM-022 Maintains or Improves BCVA & CST Through 2 Years

OPTIC Gene Therapy in nAMD

Mean BCVA (90% CI) by Cohort and Week

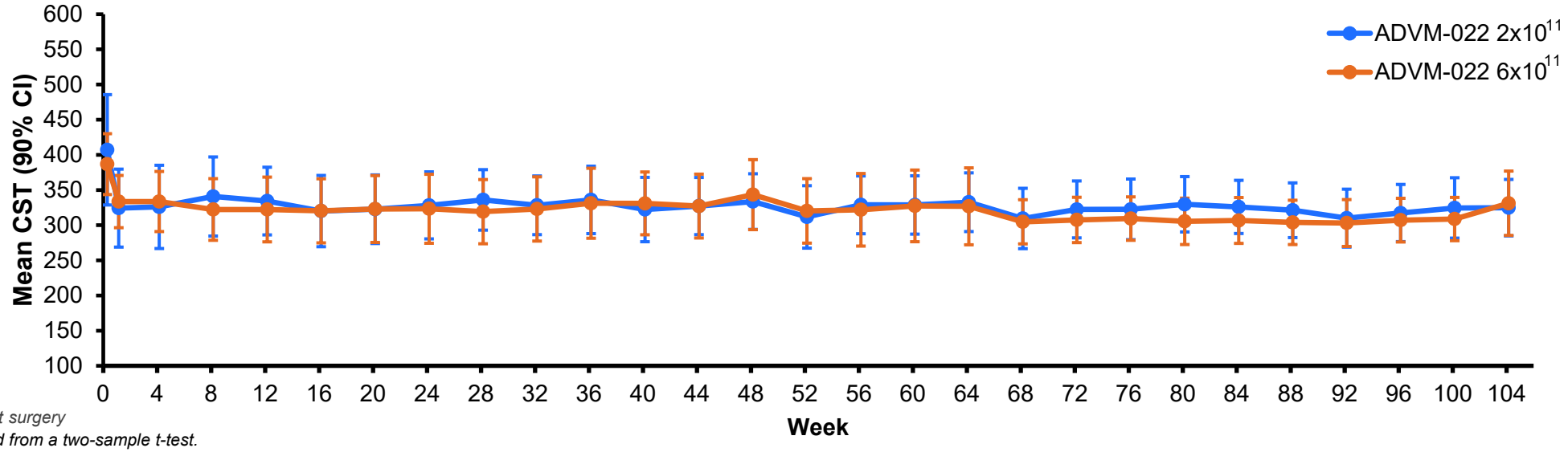


Mean BCVA (letters) change from baseline to last visit (90% CI)

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

-0.4 (-3.5, 2.7)
6x10^{11} vg/eye

Mean CST (90% CI) by Cohort and Week



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

-60.2 (-99.1, -21.3)
p = 0.017**
6x10^{11} vg/eye

-92.9 (-153.3, -32.5)
p = 0.017**
2x10^{11} vg/eye

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

Final 2-Year Analysis

Central Retinal Thickness Fluctuations Have Been Associated With Poorer Visual Outcomes[1-4]

OPTIC Gene Therapy in nAMD

Impact of macular fluid volume fluctuations on visual acuity during anti-VEGF therapy in eyes with nAMD

Usha Chakravarthy[1] · Moshe Havilio[2] · Annie Syntosi[3] · Natasha Pillai[4] · Emily Wilkes[5] · Gidi Benyamini[2] · Catherine Best[3] · Alexandros Sagkriotis[3]

Central retinal thickness fluctuations in patients treated with anti-VEGF for neovascular age related macular degeneration

Francesco Ciucci[1], Giuseppina Ioele[2], Antonio Bardocci[1], Giorgio Lofoco[1], Barbara Antonelli[1], Cristiano De Gaetano[1], Gabriele Polimanti[1], Michele De Luca[2], Gaetano Ragno[2] and Roberto Gattegna[3]

JAMA Ophthalmology | Original Investigation

Associations of Variation in Retinal Thickness With Visual Acuity and Anatomic Outcomes in Eyes With Neovascular Age-Related Macular Degeneration Lesions Treated With Anti-Vascular Endothelial Growth Factor Agents

Rebecca N. Evans, MSc; Barnaby C. Reeves, DPhil; Maureen G. Maguire, PhD; Daniel F. Martin, MD; Alyson Muldrew, PhD; Tunde Peto, MD, PhD; Chris Rogers, PhD; Usha Chakravarthy, MD, PhD

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Fluctuations in Macular Thickness in Patients with Retinal Vein Occlusion Treated with Anti–Vascular Endothelial Growth Factor Agents

Andrew X. Chen, BSE,[1,2] Tyler E. Greenlee, DO,[2] Thais F. Conti, MD,[2] Isaac N. Briskin, MA,[3] Rishi P. Singh, MD[1,2]

[1]Evans, et al. JAMA Ophthalmol. 2020;138(10):1043-1051. [2]Chen, et al. Ophthalmol Retina. 2020;4:1158-1169.
[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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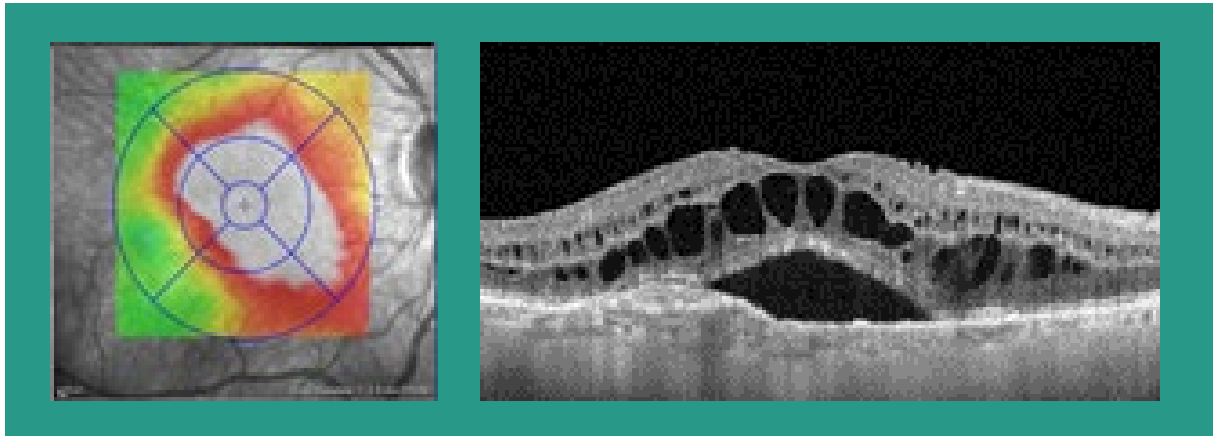
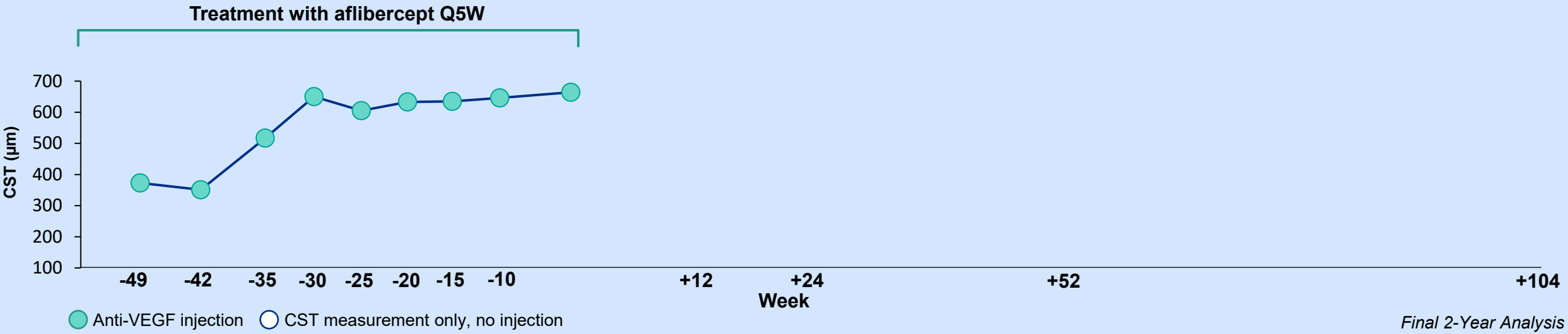
Case Study: 81-year-old Male With 19 IVTs Prior to Study

Cohort 3 ($2x10^{11}$ vg/eye) Participant



Persistent fluid despite frequent anti-VEGF injections

(Baseline) -2 Weeks, BCVA: 75 letters, CST: 664 µm

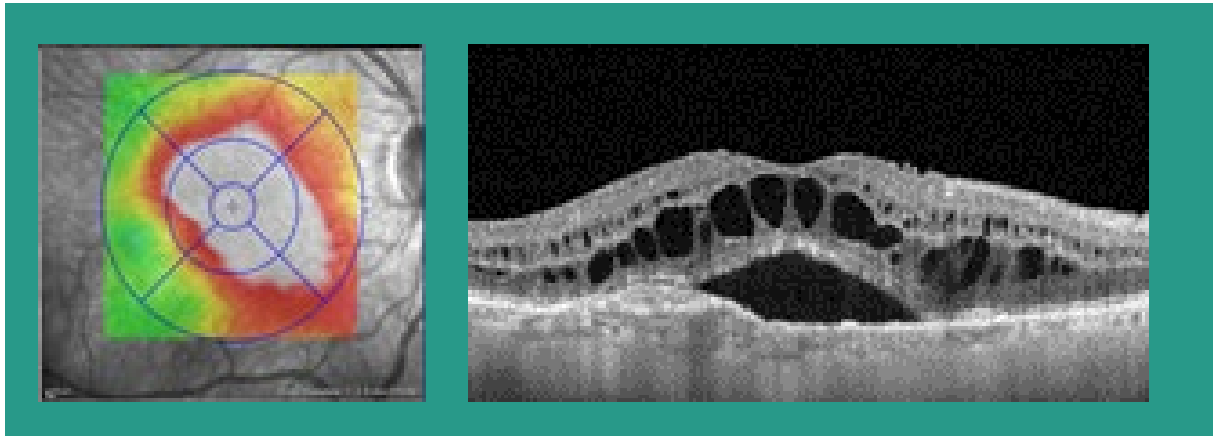


Final 2-Year Analysis

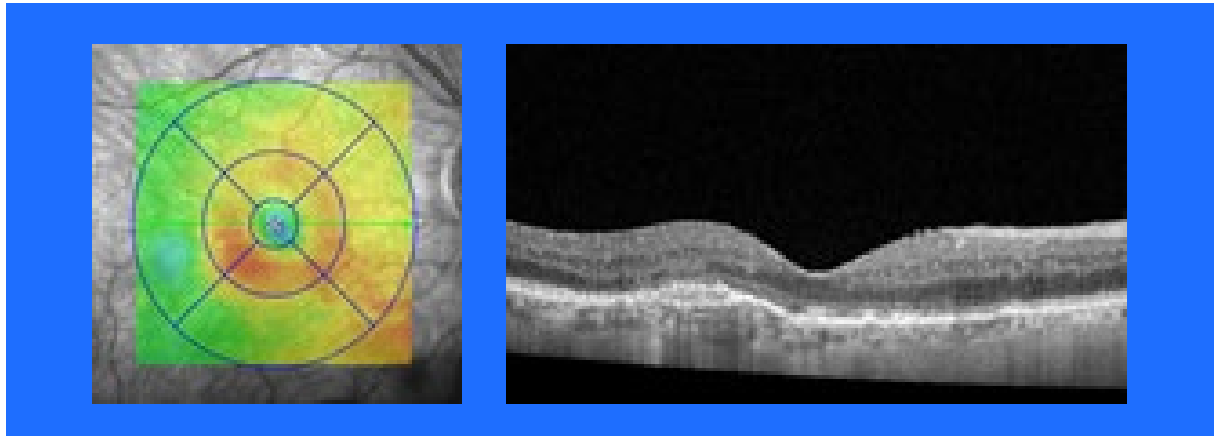
Case Study: 81-year-old Male With 19 IVTs Prior to Study and No Supplemental Anti-VEGF Injections After Ixo-vec - 2e11 vg/eye

OPTIC Gene Therapy in nAMD

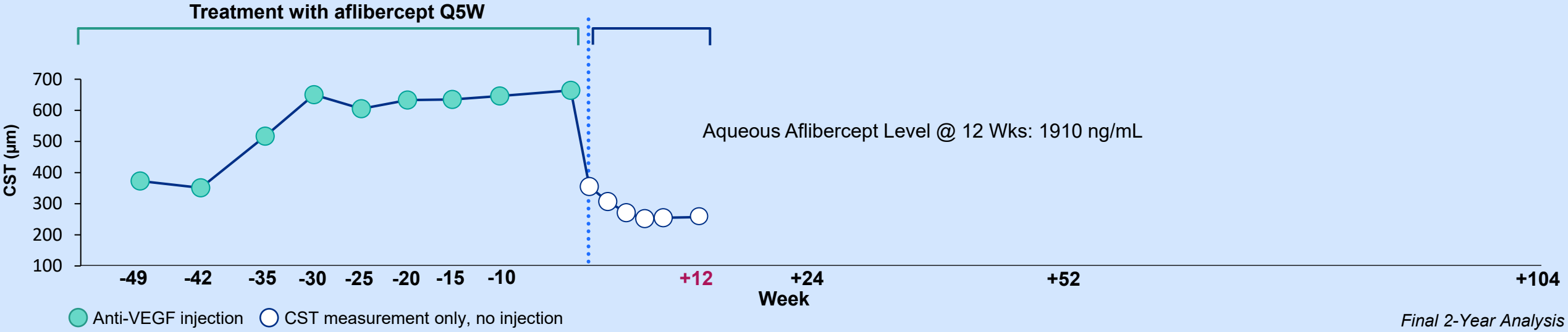
Cohort 3 ($2x10^{11}$ vg/eye) Participant



(Baseline) -2 Weeks, BCVA: 75 letters, CST: 664 µm



+12 Weeks, BCVA: +6 letters, CST: -407 µm

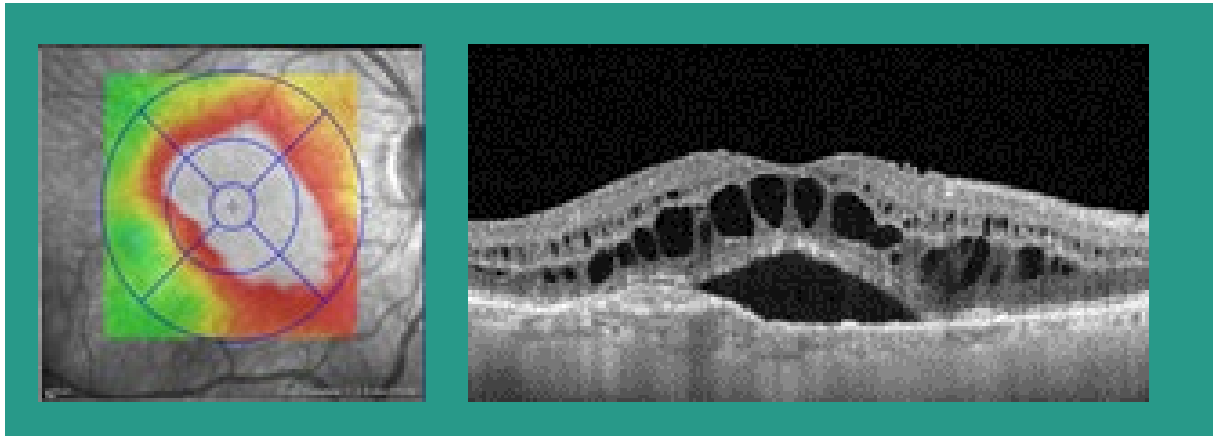


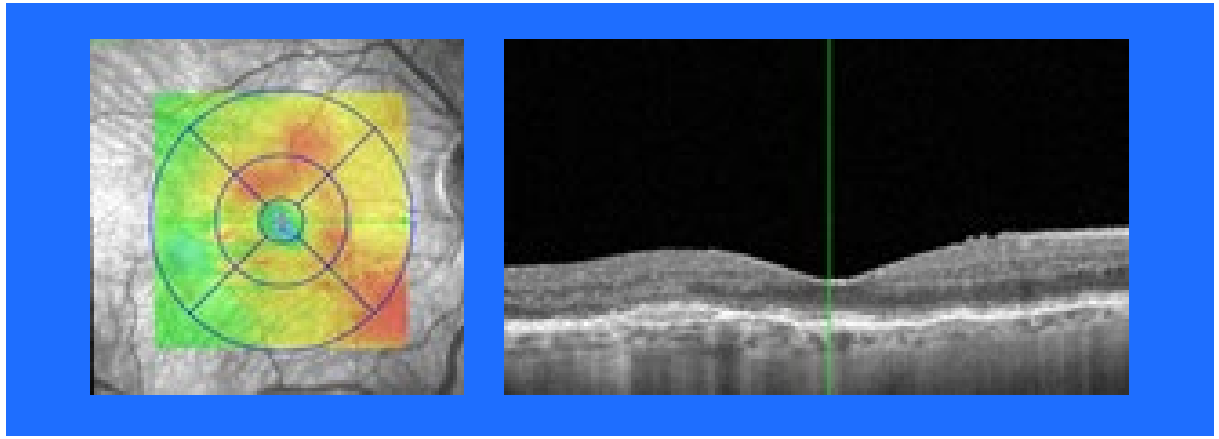
Final 2-Year Analysis

Case Study: 81-year-old Male With 19 IVTs Prior to Study and No Supplemental Anti-VEGF Injections After Ixo-vec - 2e11 vg/eye

OPTIC Gene Therapy in nAMD

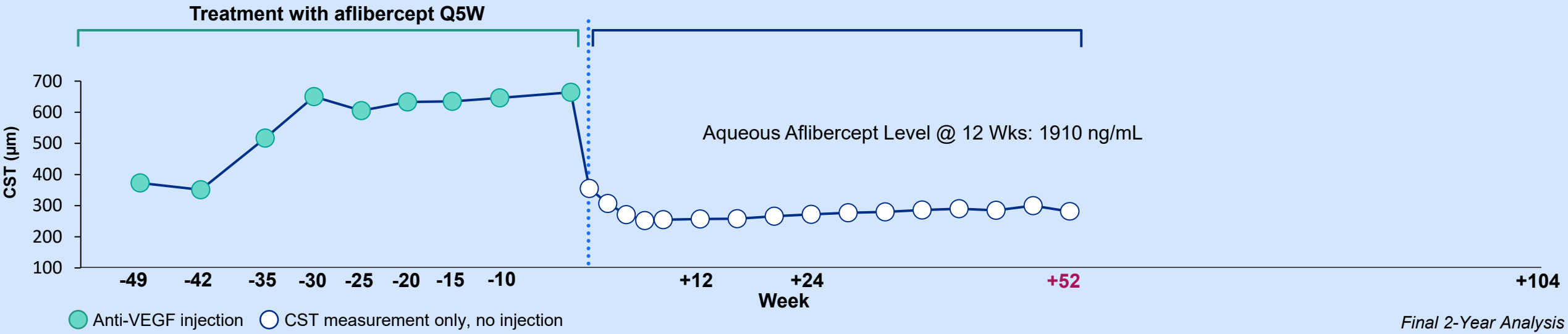
Cohort 3 ($2x10^{11}$ vg/eye) Participant





(Baseline) -2 Weeks, BCVA: 75 letters, CST: 664 µm

+52 Weeks, BCVA: +8 letters, CST: -383 µm

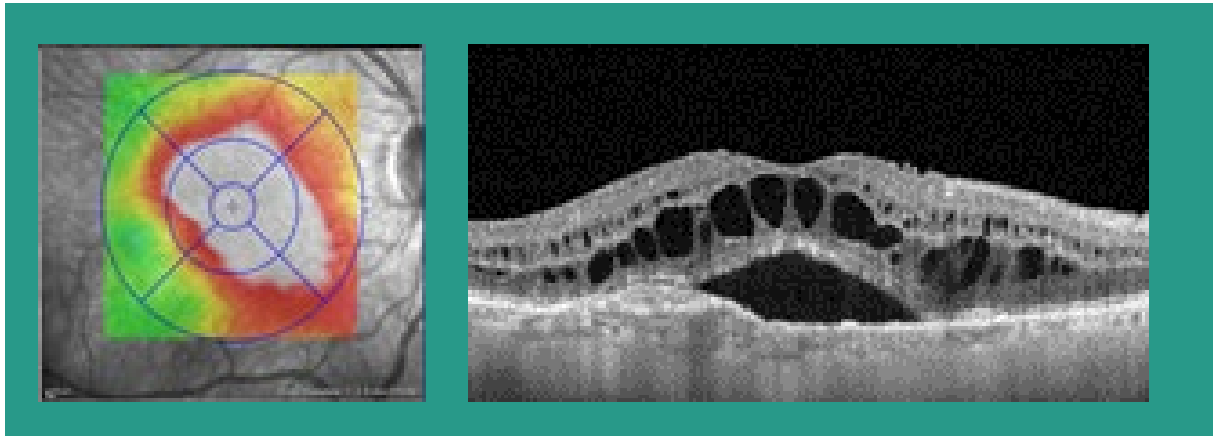


Final 2-Year Analysis

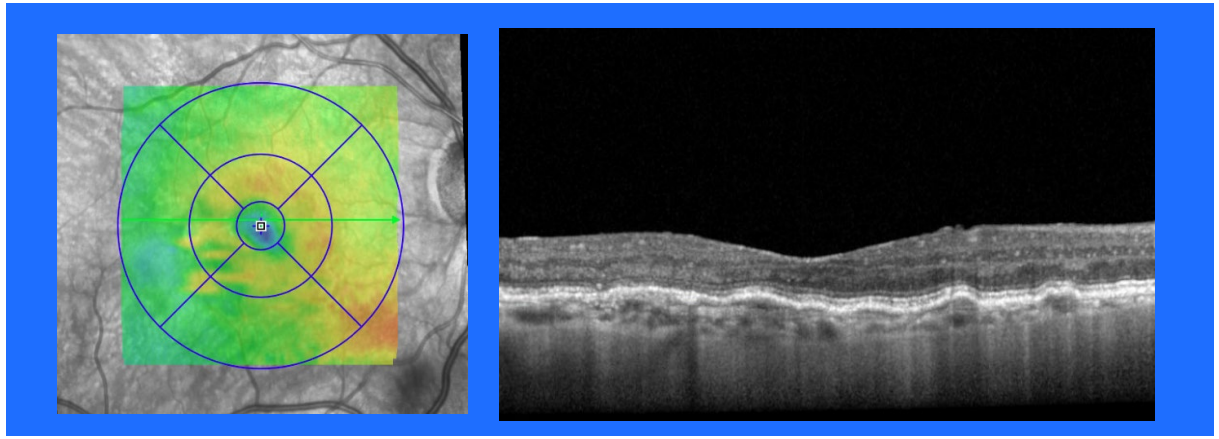
Case Study: 81-year-old Male With 19 IVTs Prior to Study and No Supplemental Anti-VEGF Injections After Ixo-vec - 2e11 vg/eye

OPTIC Gene Therapy in nAMD

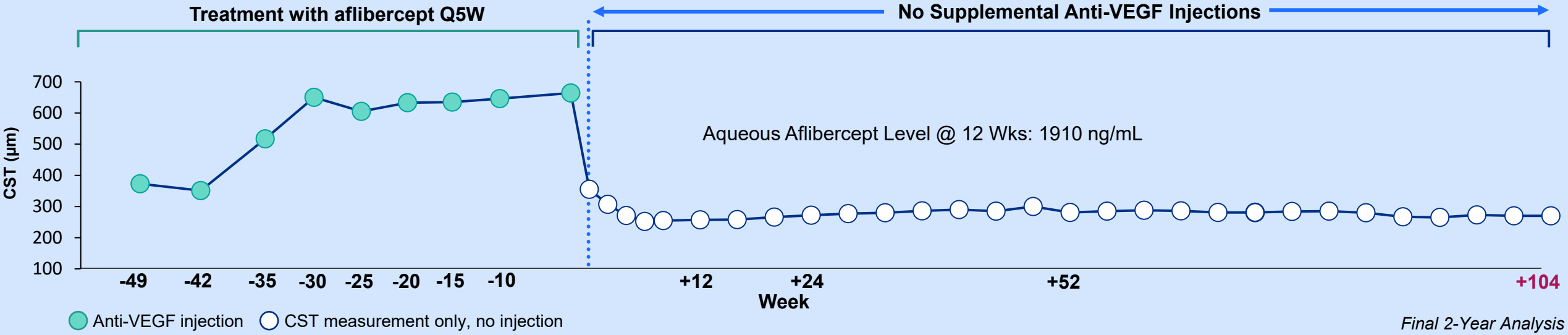
Cohort 3 ($2x10^{11}$ vg/eye) Participant



(Baseline) -2 Weeks, BCVA: 75 letters, CST: 664 µm

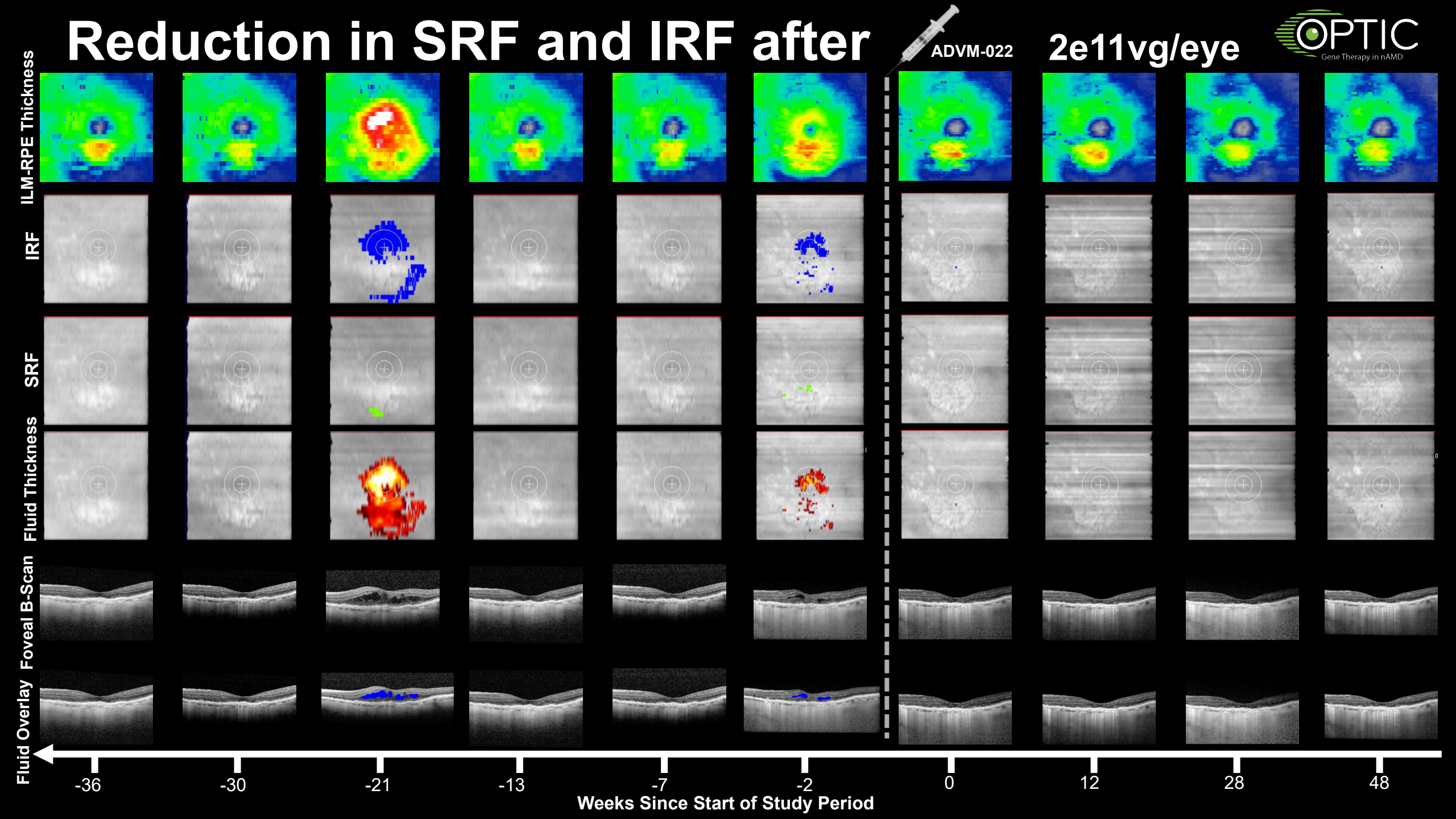


+104 Weeks, BCVA: +9 letters, CST: -394 µm



Final 2-Year Analysis

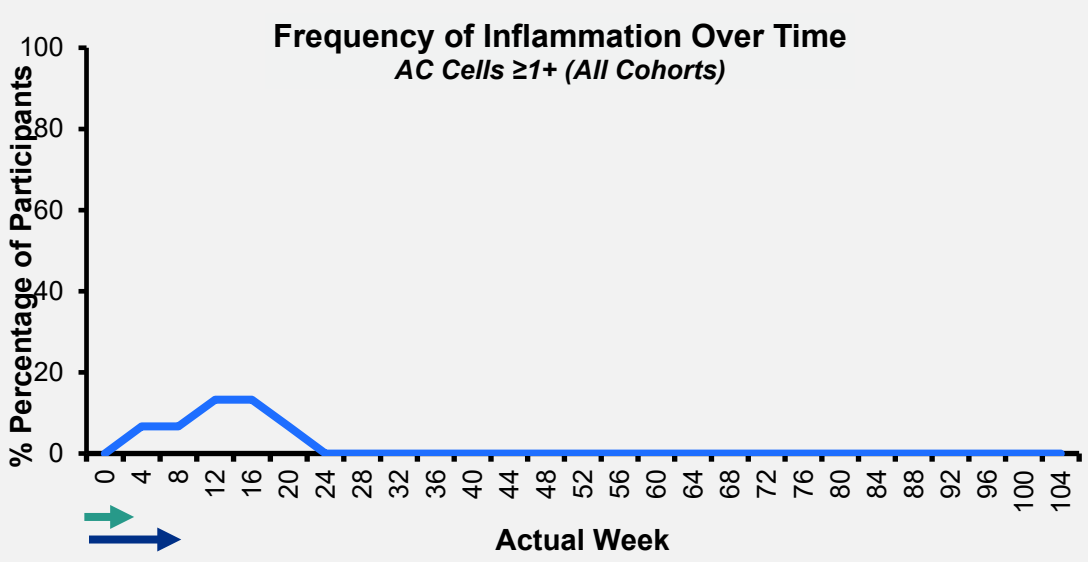
Reduction in SRF and IRF after ADVM-022 2e11vg/eye

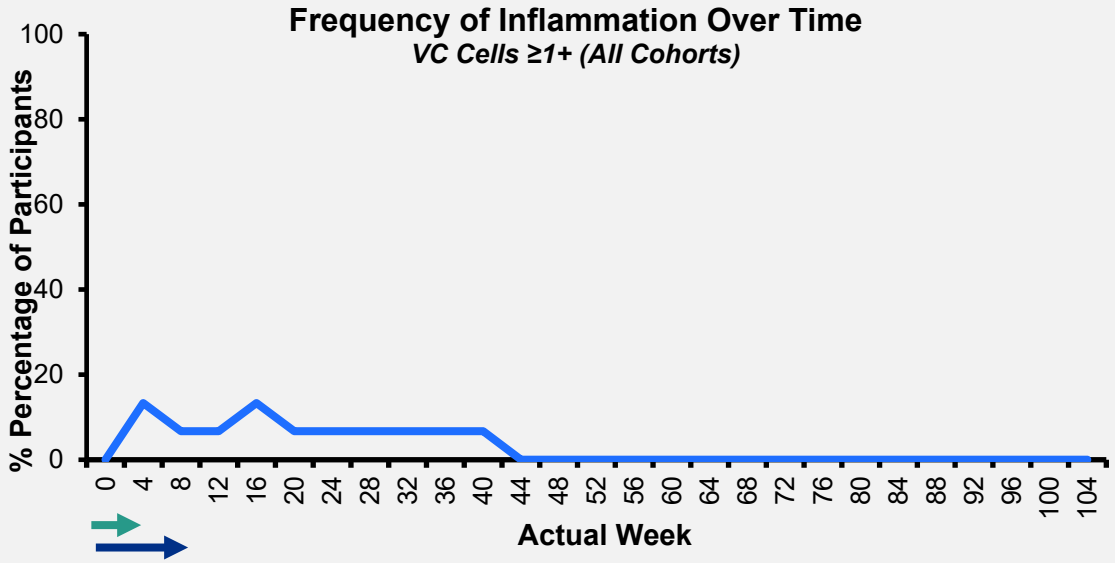


Ixo-vec Has a Manageable Safety Profile

- Despite short prophylactic corticosteroid, ADVM-022 was generally well tolerated
- **Most common AEs are dose-dependent, mild to moderate* inflammation responsive to topical corticosteroids and resolved in all patients at 2e11 vg/eye at end of study**
- ADMV-022 related SAEs were reported: uveitis (responsive to topical corticosteroids) and dry AMD
- No vasculitis, retinitis, choroiditis, vascular occlusions or endophthalmitis
- No clinically relevant low IOP observed at any dose

Mild Inflammation at ADVM-022 2x10^{11} vg/eye





Corticosteroid prophylactic regimen: 13 days oral prednisone or 6 weeks of topical drops

**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*
AC, aqueous cells; VC, vitreous cells. Final 2 Year Analysis 2022.

Ixo-vec Phase 2

IVT Gene Therapy for the Treatment of wet AMD

LUNA

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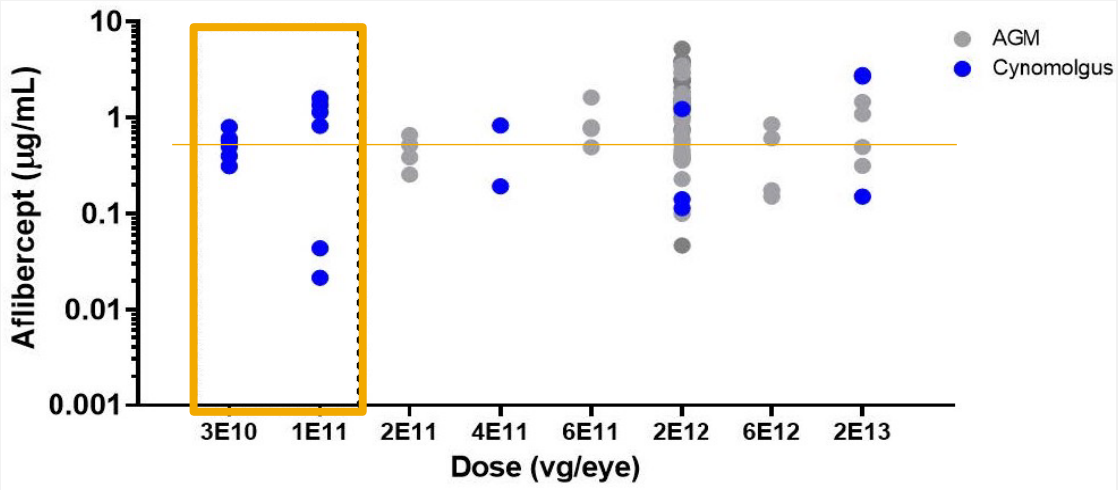
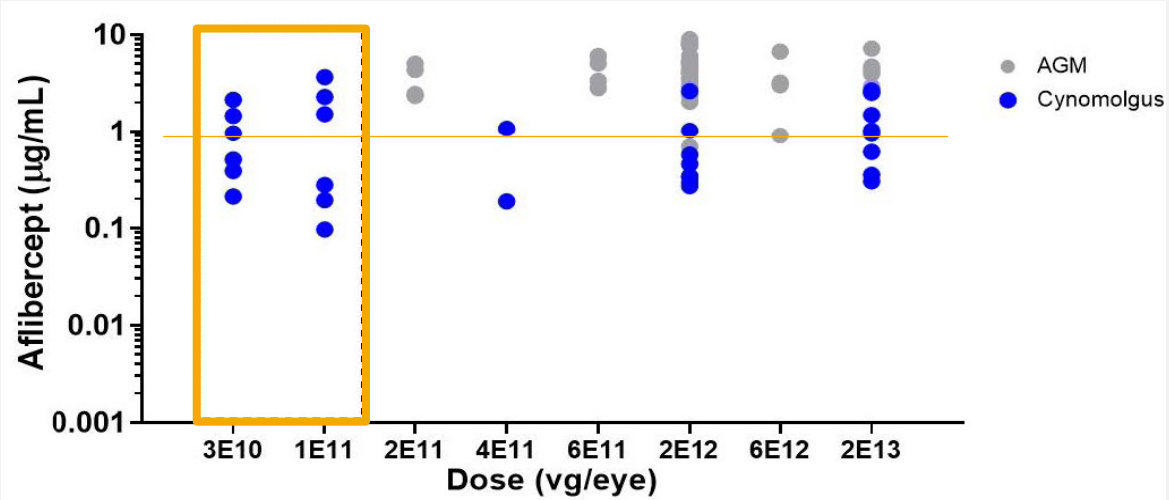
LUNA Dose Selection: NHP Data Support Efficacy and Tolerability of Human Equivalent Dose of 6E10 of Ixo-vec

ADVM-022 at doses as low as 3E10 in NHP (HDE dose of 6E10) predicts therapeutic levels of aflibercept

Aqueous Humor



Vitreous Humor



Historical data shows a near flat dose response over 3 logs. Historical NHP studies in support of ADVM-022 included African green monkeys (AGM, grey) or cynomolgus (blue). NHPs were administered ADVM-022 at doses spanning nearly 3 logs (3E10 – 2E13 vg/eye). Peak aflibercept levels for each NHP subject in each study were measured via aflibercept ELISA and recorded. The samples from the current study are outlined with dotted boxes.

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Ixo-vec Well Tolerated in NHP Without Prophylaxis - NOAEL 1e11 vg/eye

Summary of ADVM-022 Tolerability

- Minimal inflammation without prophylaxis
- No adverse clinical signs
- Dose-dependent, non-adverse slight to mild inflammation characterized by pigment and cells in the VH.
- NOAEL has been determined at 1e11 vg/eye (HED 2e11 vg/eye).

ADVM-022 Treatment	NHP ID	Day 0	Day 3	Day 8	Day 15	Day 21	Day 25	Day 36	Day 50	Day 64	Day 78	Day 92
Vehicle	1001 OD	0	0	0	0	0	0	0	0	0	0	0
	1001 OS	0	0	0	0	0	0	0	0	0	0	0
	1002 OD	0	0	0	0	0	0	0	0	0	0	0
	1002 OS	0	0	0	0	0	0	0	0	0	0	0
3E+10	2001 OD	0	0	0	0	0	0	0	0	0	0	0
	2001 OS	0	0	0	0	0	0	1	1	0.5	0	0
	2002 OD	0	0	0	0	0	0	0	0	0	0	0
	2002 OS	0	0	0	0	0	0	0	0	0	0	0
	2103 OD	0	0	0	0	0	0	0	0	0	0	0
	2103 OS	0	0	0	0	0	0	0	0	0	0	0
	2004 OD	0	0	0	0	0	0	0	0	0	0	0
	2004 OS	0	0	0	0	0	0	0	0	0	0	0
1E+11	3001 OD	0	0	0	0	0	0	0	0	0	0	0
	3001 OS	0	0	0	0	0	0	0	0	0	0.5	0.5
	3002 OD	0	0	0	0	0	0	0	0	0	0	0
	3002 OS	0	0	0	0	0	0	0	0	0	0	0
	3003 OD	0	0	0	0	0	2	2	2	0.5	0.5	0
	3003 OS	0	0	0	0	0	0	2	2	0.5	0.5	0
	3004 OD	0	0	0	0	0	0	2	2	2	1	1
	3004 OS	0	0	0	0	0	1	2	2	2	1	1

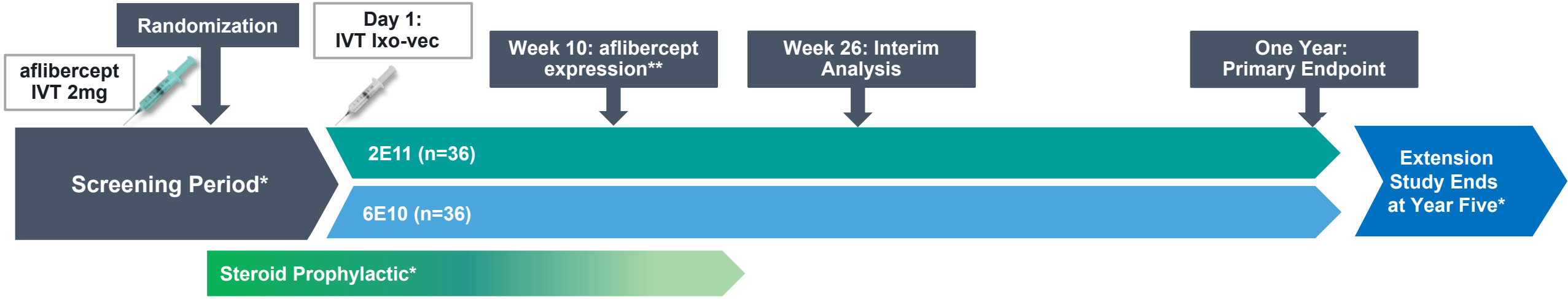
Color Codes
4
3
2
1
0.5
0

Non-Clinical Data Support Efficacy and Tolerability of a Human Equivalent Dose of 6E10 vg/eye of ADVM-022 for the Treatment of Neovascular Age-Related Macular Degeneration. The American Society of Gene and Cell Therapy 2022.

ADVERUM

LUNA Phase 2 Study in Wet AMD

Objective: The LUNA trial is a multicenter, double-masked, randomized, parallel-group Phase 2 study evaluating a one-time IVT injection of either of two doses of Ixo-vec (ADVM-022), including $2x10^{11}$ vg/eye (2E11) dose and a new, lower $6x10^{10}$ vg/eye (6E10) dose in 72 patients.



Prophylactic Regimens

Study Population

- Wet AMD diagnosis
- 50 years or older
- Demonstrated response to anti-VEGF treatment

Durezol® topical (n=18)

Ozurdex® IVT (n=18)

Durezol® topical + Prednisone (n=18)

Ozurdex® IVT + Prednisone (n=18)

Primary Endpoints

- Mean change in best corrected visual acuity (BCVA) from baseline to one year
- Incidence and severity of adverse events

Secondary Objectives

- Assess effectiveness of prophylactic steroid regimens on minimizing inflammation and recurrence
- Evaluate the effect of Ixo-vec on central subfield thickness (CST)

Study timeline and length of arrows depicted not to scale. Additional levels of aflibercept expressions will be measured throughout.*

Ixo-vec Granted Priority Medicines (PRIME) Designation for the Treatment of wet AMD by the European Medicines Agency

- PRIME program is to enhance support for research on and development of medicines that target a significant unmet medical need
- Only ophthalmology GTx in non rare disease with existing standard of care to be granted PRIME designation[1]

EUROPEAN MEDICINES AGENCY
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Excerpts from CHMP's assessment of ADVM-022 PRIME application:

> *An **unmet medical need is agreed**. Given the scale of the affected nAMD population and limitations in currently available treatment options resulting in sub-optimal real world visual outcome...*
>
> *Whilst acknowledging the need for further optimisation of the immunosuppression protocols, overall, **the available data support the product's potential to address the unmet medical need in nAMD** **by providing for continuous expression of aflibercept after a single administration and relieving patients from the treatment burden of frequent intravitreal injections**.*

[1]https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines, Accessed on August 8, 2022


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