Addressing Unmet Needs For Patients with Wet AMD

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Eyecelerator

October 17th 2024

ADVERUM
Preserving Sight for Life®

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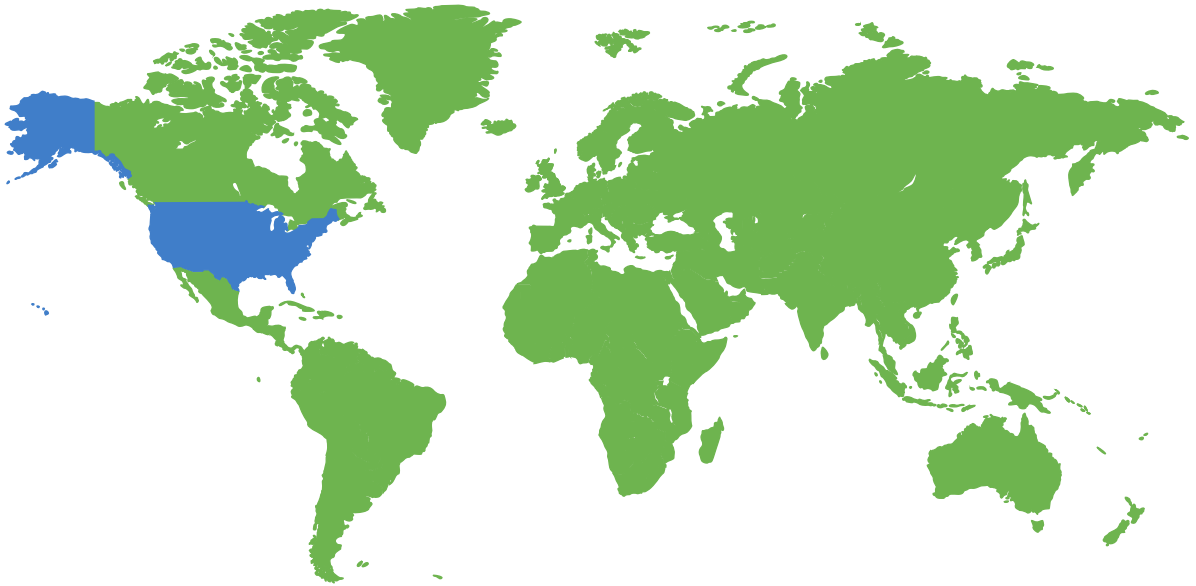
1.5M patients U.S.[1,2] **20M** worldwide.[1,2]

~200,000 new cases every year.[1,2]

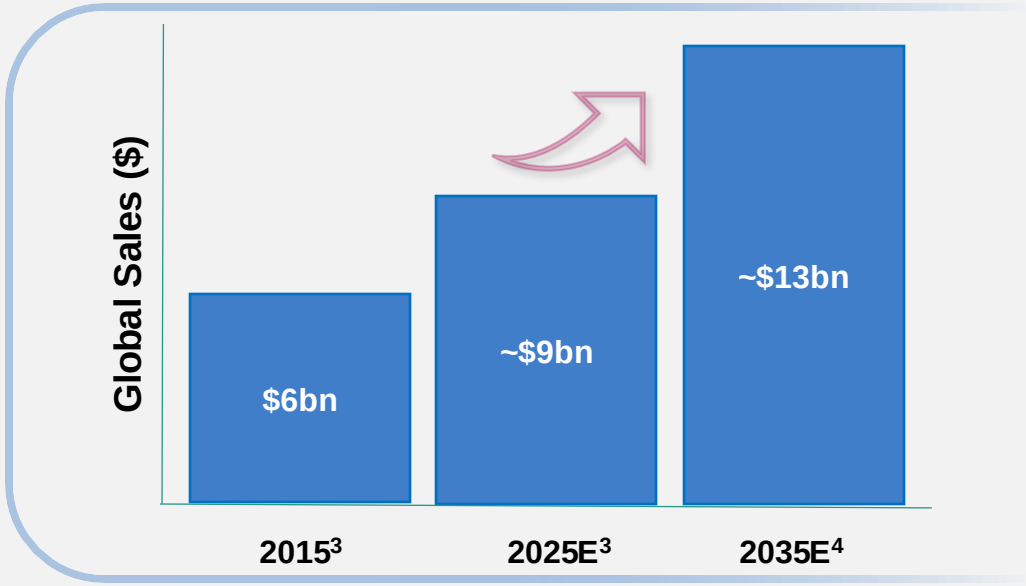


Up to 42% develop bilateral disease within 2-3 years of initial diagnosis[5]

Wet AMD Global Market
Expected to Grow to $13bn by 2035[4]

Wet AMD Global Market Opportunity

Market growth driven by aging population and product innovation



1% market share ~ $260M to $440M

(assuming 3-5-year benefit of gene therapy)

[1]Bright Focus Foundation. Age-Related Macular Degeneration: 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 [3] 2023 Cowen Equity Research – Therapeutic Categories Outlook [4] Company estimates [5]Gangnon RE et al. (2015) JAMA Ophthalmol; 133 (2): 125–132. Rasmussen A. et al., (2017) Eye 31, 978–980 (2017). Wong TY, et al. (2020) Retina. 40, 599-611 Zarranz-Ventura J et al. (2014). Ophthalmology; 121 (10): 1966–1975.

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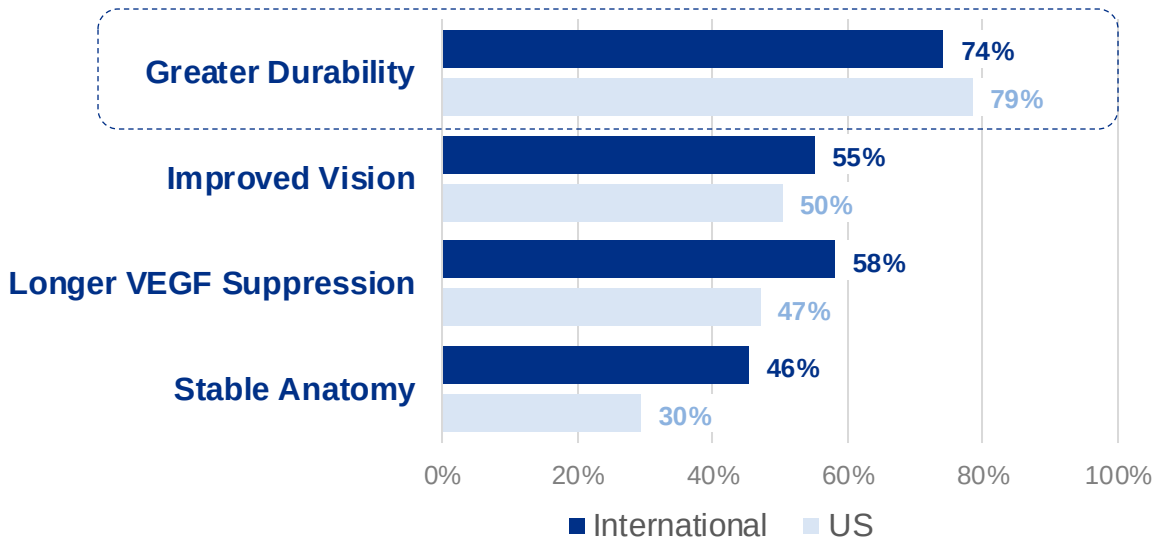
Current therapies for wet AMD require ***frequent intravitreal injections*** that are burdensome to patients and caregivers, impacting treatment compliance and clinical outcomes

Therapies with ***greater durability*** continue to be top of mind for physicians as significant unmet need

Patient Adherence Can Be Limited By[1,2]

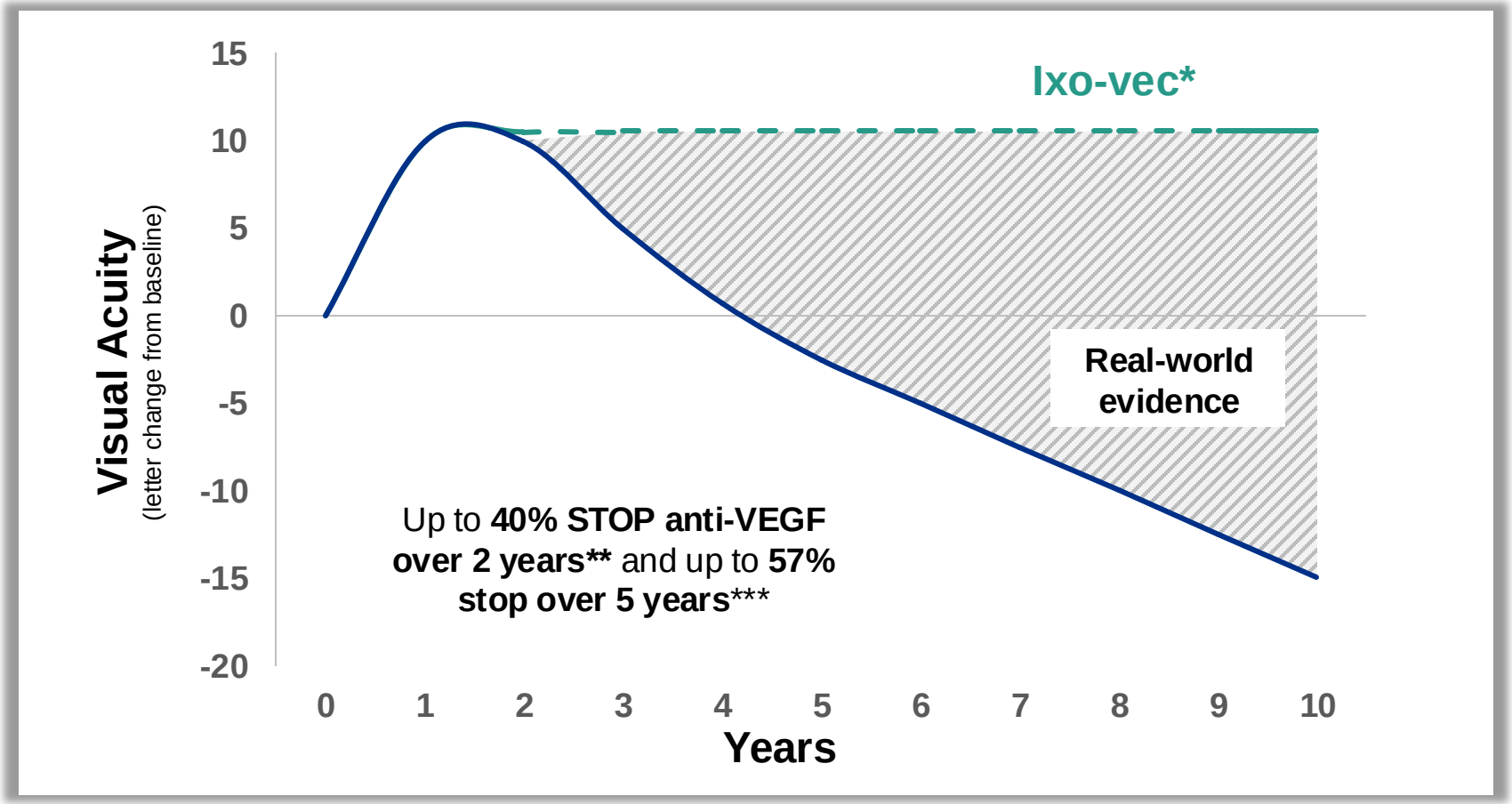
- Needle Anxiety
- Financial Hardship
- Scheduling Conflicts
- Lack of Transportation

Physician Survey: Greatest Unmet Needs In Treating Wet AMD And DME[3]



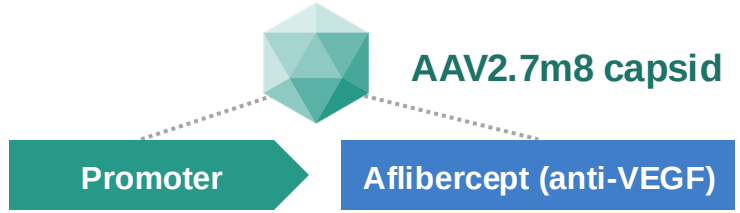
Sources: [1]Hussain RM, Shaukat BA, Ciulla LM, Berrocal AM, Sridhar J. Vascular Endothelial Growth Factor Antagonists: Promising Players in the Treatment of Neovascular Age-Related Macular Degeneration. Drug Des Devel Ther. 2021 Jun 21;15:2653-2665. doi: 10.2147/DDDT.S295223. PMID: 34188445; PMCID: PMC8232378., [2]Polat O, İnan S, Özcan S, Doğan M, Küsbeci T, Yavaş GF, İnan ÜÜ. Factors Affecting Compliance to Intravitreal Anti-Vascular Endothelial Growth Factor Therapy in Patients with Age-Related Macular Degeneration. Turk J Ophthalmol. 2017 Aug;47(4):205-210. doi: 10.4274/tjo.28003. Epub 2017 Aug 15. PMID: 28845324; PMCID: PMC5563548., [3]ASRS 2023 Preferences and Trends Survey.

Illustrative Long-Term Vision Outcome

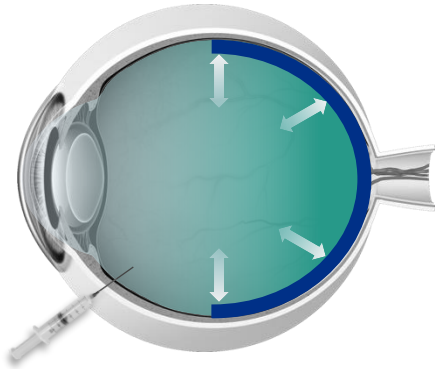


*SoC curve is based on CATT, HARBOR, and 7UP extension out to 5 years, with years 5-10 modeled. Sources: Weng CY, Singh RP, Gillies MC, Regillo CD. Optimizing Visual Outcomes in Patients With Neovascular Age-Related Macular Degeneration: the Potential Value of Sustained Anti-VEGF Therapy. Ophthalmic Surg Lasers Imaging Retina. 2023 Nov;54(11):654-659, *Potential Ixo-vec curve illustrated based on OPTIC results Khanani et al. Lancet eClinical Medicine -- THE LANCET Discovery Science 2024. **Wykoff CC, Garmo V, Tabano D, et al. Impact of Anti-VEGF Treatment and Patient Characteristics on Vision Outcomes in Neovascular Age-related Macular Degeneration: Up to 6-Year Analysis of the AAO IRIS® Registry. Ophthalmol Sci. 2023;4(2):100421. ***Boulanger-Scemama E, et al. Ranibizumab for exudative age-related macular degeneration: A five year study of adherence to follow-up in a real-life setting. J Fr Ophtalmol. 2015;38:620–7.*

Codon optimized aflibercept-encoding AAV2.7m8 vector engineered via directed evolution to enhance retinal transduction



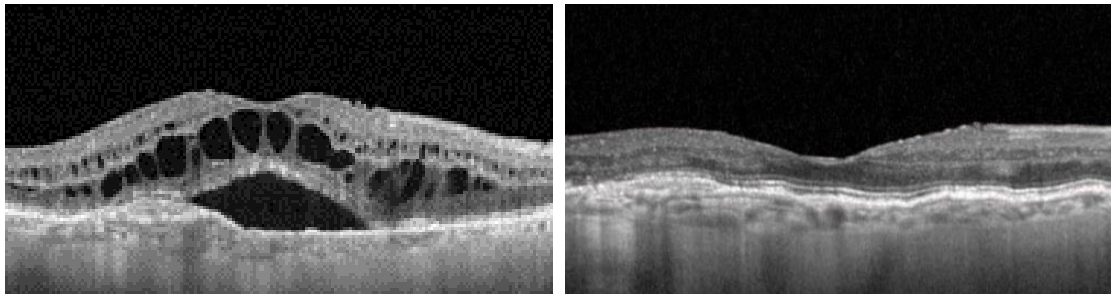
A one-time Ixo-vec IVT injection transduces retinal cells to become a biofactory continually producing aflibercept



IVT injection of Ixo-vec

115 participants dosed with Ixo-vec across 3 clinical trials with up to 5 years of follow-up

nAMD OPTIC 2E10 Participant with No Supplemental anti-VEGF Injections through 3 Years[3]



Baseline
BCVA (ETDRS): 75

Year 3
BCVA (ETDRS): 80

IVT: intravitreal; FIH: first-in-human
[1]Grishanin, R, et al. Molecular Ther 2019; 27(1), 118-129; [2]Khanani AM et al. Lancet eClinical Medicine. 2024; [3]Regillo CD. AAO Annual Meeting 2023. San Francisco, CA

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Primary Objective

Long-term safety and efficacy of Ixo-vec IVT in treatment experienced patients

Secondary Objectives

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

	Ixo-vec Dose	Corticosteroid Prophylaxis	Extension Scheduled Visits	Supplemental Aflibercept (2 mg IVT) Criteria:
Cohort 1 (n=6)	6E11	Oral*, 13d	Quarterly assessments following completion of 2-year OPTIC parent study	• ≥10 letters BCVA (ETDRS) loss m baseline **OR,** • CST >75 µm increase from baseline **OR,** • New Vision-threatening hemorrhage due to AMD • After initial supplemental injection subsequent injections administered at investigator discretion
Cohort 2 (n=6)	2E11	Oral*, 13d		
Cohort 3 (n=9)	2E11	Eye Drops**, 6 wks		
Cohort 4 (n=9)	6E11	Eye Drops**, 6 wks		

*Study timelines not to scale. *Participants in Cohorts 1 and 2 received prophylaxis of 60 mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper; participants in Cohorts 3 and 4 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; IRF, intraretinal fluid; SRF, subretinal fluid; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT, intravitreal therapy; QID, four times daily; SD-OCT, spectral domain optical coherence tomography; OPTIC: NCT03748784; OPTIC EXT: NCT04645212.*

Baseline Characteristics	Cohort 1: 6E11 OPTIC (N=6) OPTIC EXT (N=4)	Cohort 2: 2E11 OPTIC (N=6) OPTIC EXT (N=4)	Cohort 3: 2E11 OPTIC (N=9) OPTIC EXT (N=8)	Cohort 4: 6E11 OPTIC (N=9) OPTIC EXT (N=7)
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)	3.3 (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 Ixo-vec	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)
Participant Status				
Follow-up (Years)	4–5 (median 4.5)	4 (median 4.0)	3–4 (median 3.7)	3 (median 3.0)

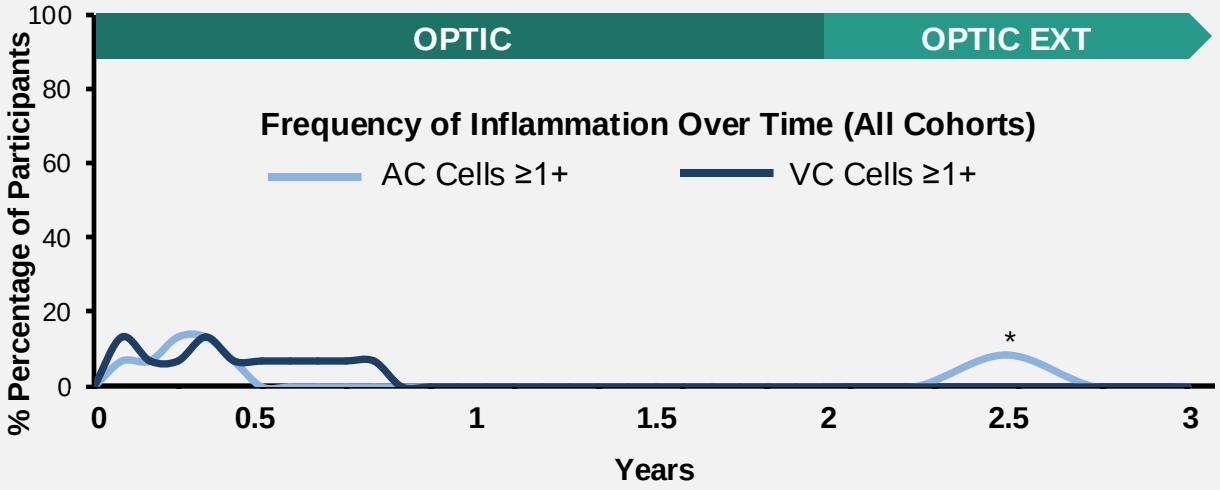
*Not including the mandated aflibercept at Screening;
BCVA, best corrected visual acuity: CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor

OPTIC 2E11 vg/eye Dose

- 2E11 was generally well tolerated through 3 years of follow-up
- Inflammation was dose-dependent, did not impact vision and, when present, was responsive to local corticosteroids
- **14** of **15 (93%) inflammation free at Year 1** and **100% at Year 2**
- **Long-term safety data** (published out to 3Y) with **10-fold safety margin from highest dose tested in nAMD**

Frequency of Inflammation Decreased Over Time

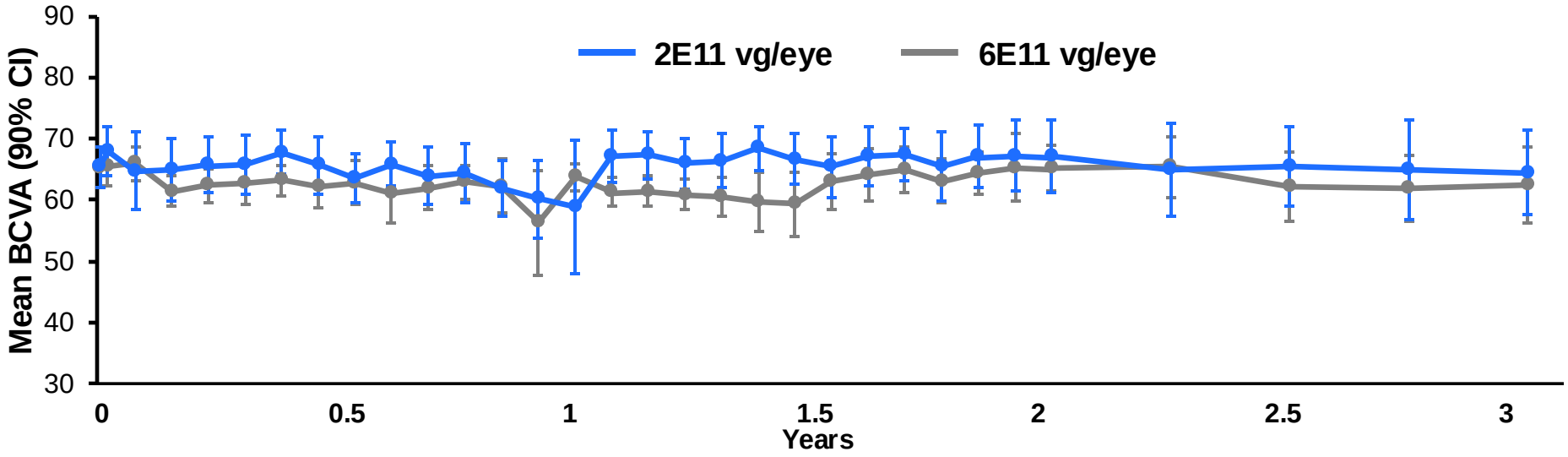
2E11 vg/eye



Insufficient prophylaxis in OPTIC

13 days oral prednisone or 6 weeks of topical drops

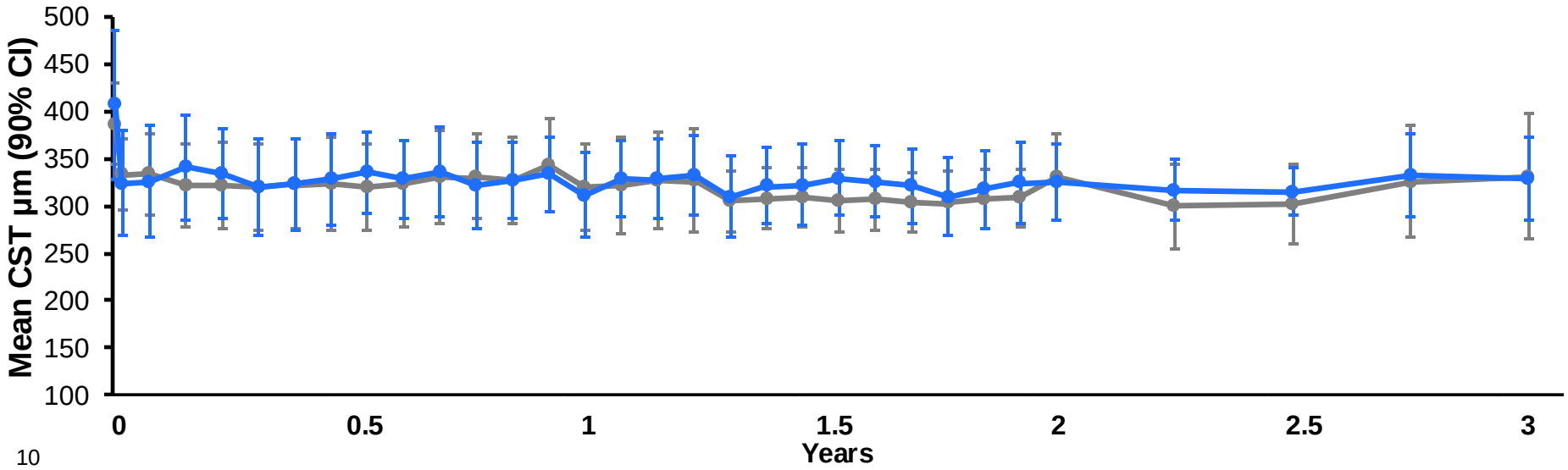
AC, aqueous cells; VC, vitreous cells.
**The 2E11 participant (n=1) with inflammation at year 2.5 underwent a cataract surgery near the start of OPTIC EXT. At the next scheduled visit (3 months later at 2.5 year visit), inflammation was detected that was responsive to topical corticosteroid.*



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

-1.6 (-7.1, 3.9)
2E11 vg/eye

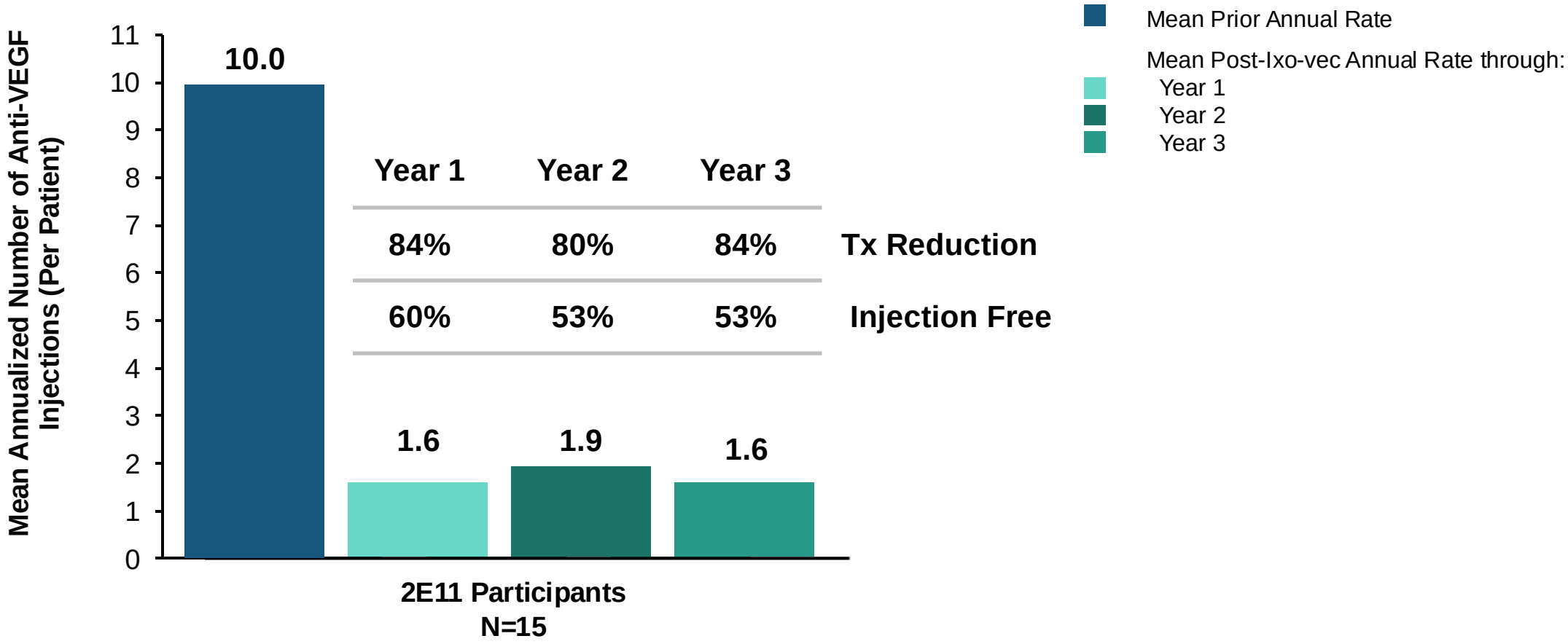
-2.4 (-6.4, 1.6)
6E11 vg/eye



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

-64.9 (-105.5, -24.2)
6E11 vg/eye

-89.7 (-164.0, -15.5)
2E11 vg/eye



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

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

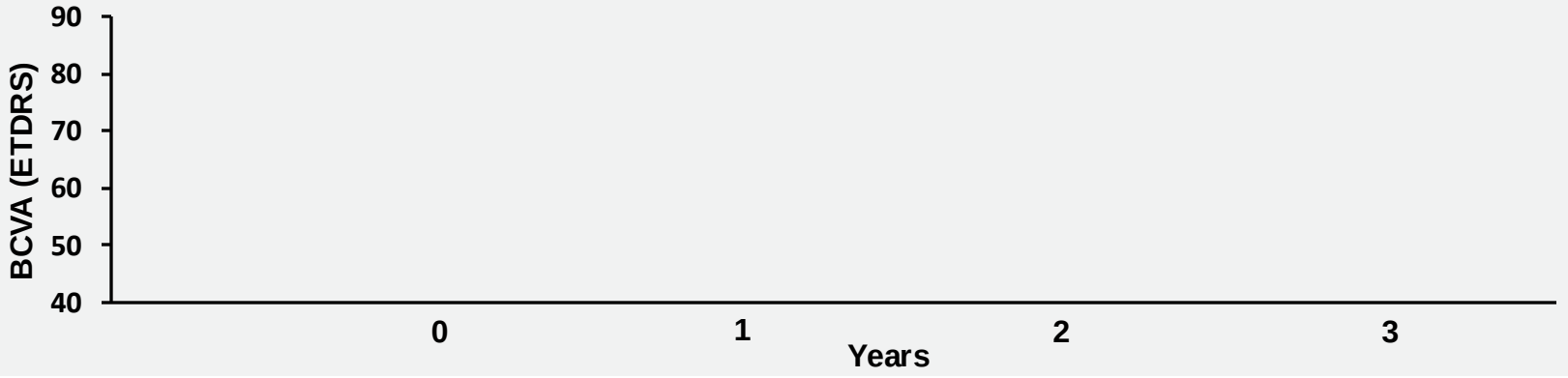
Fluctuations in Macular Thickness in Patients with Retinal Vein Occlusion Treated with Anti–Vascular Endothelial Growth Factor Agents

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]

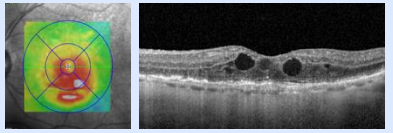
[1]Evans, et al. JAMA Ophthalmol. 2020;138(10):1043-1051. [2]Chen, et al. Ophthalmol Retina. 2020;4:1158-1169.
[3]Ciucci, et al. EUR J Ophthalmol 2021 Aug 14;11206721211037820.2021. [4]Chakravarthy, et al. Eye (2021) 35:2983–2990.

90-Year-Old Female with 9 IVTs in the 12 Months Prior to Ixo-vec

Aflibercept Q5W prior to Ixo-vec

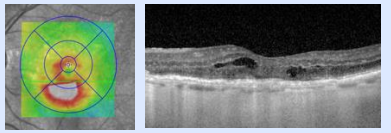


-56 weeks



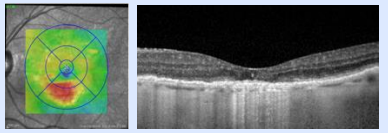
-2 wks (baseline)

BCVA: 53 letters
CST: 358 µm



Day 0

Ixo-vec administration

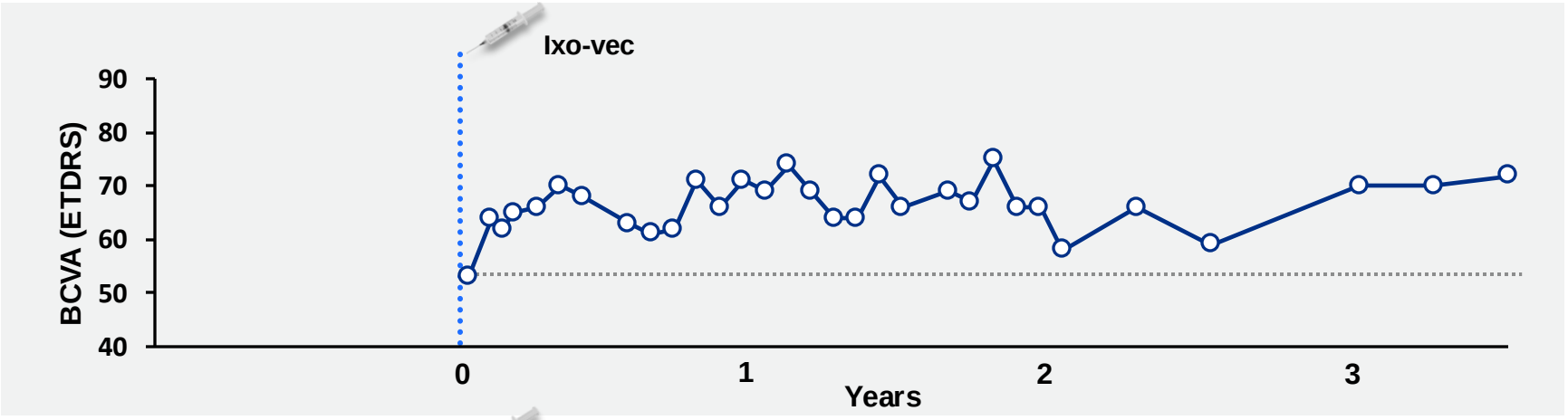


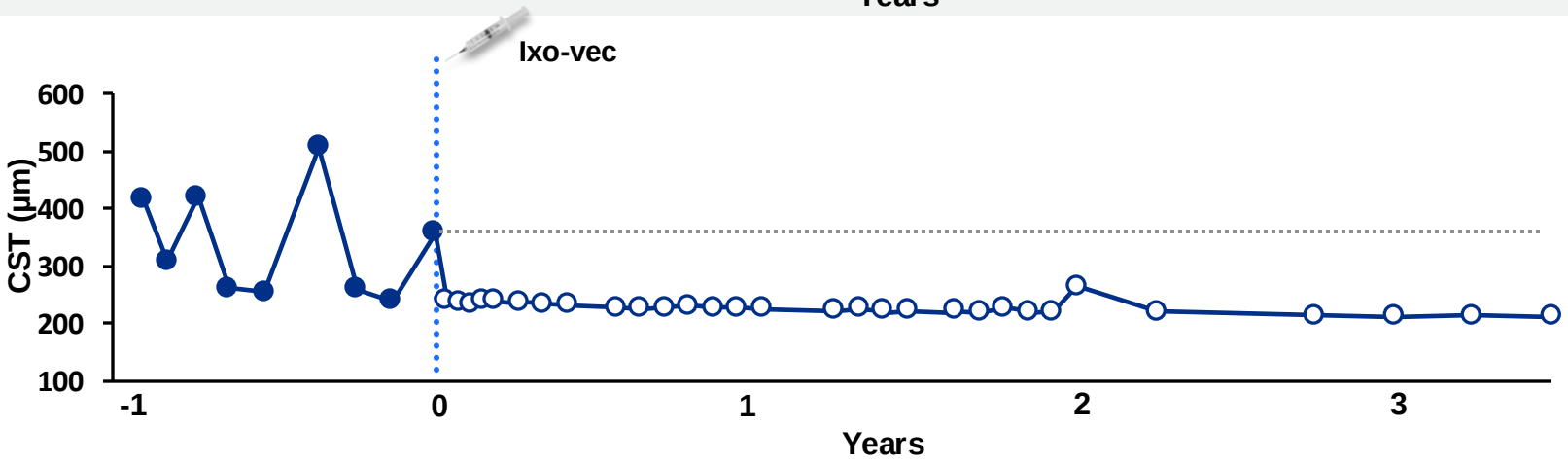
Anti-VEGF injection Study visit, no supplemental injection Baseline

Data cut: 23Aug2023

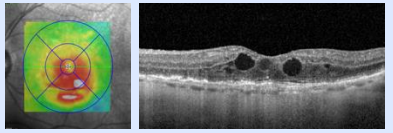
90-Year-Old Female with 9 IVTs in the 12 Months Prior to Ixo-vec

Aflibercept Q5W prior to Ixo-vec | **100% anti-VEGF injection free following Ixo-vec**



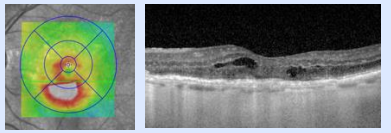


-56 weeks



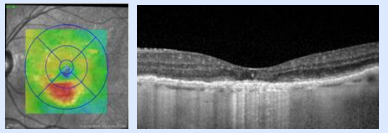
-2 wks (baseline)

BCVA: 53 letters
CST: 358 µm



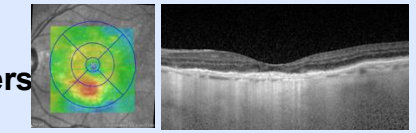
Day 0

Ixo-vec administration



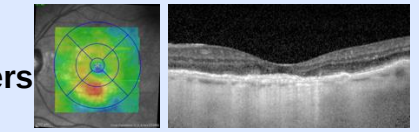
9 Months

BCVA Δ: +18 letters
CST Δ: -127 µm



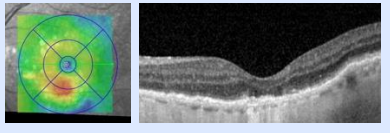
1 Year

BCVA Δ: +16 letters
CST Δ: -132 µm



2 Years

BCVA Δ: +5 letters
CST Δ: -93 µm



2.2 Years

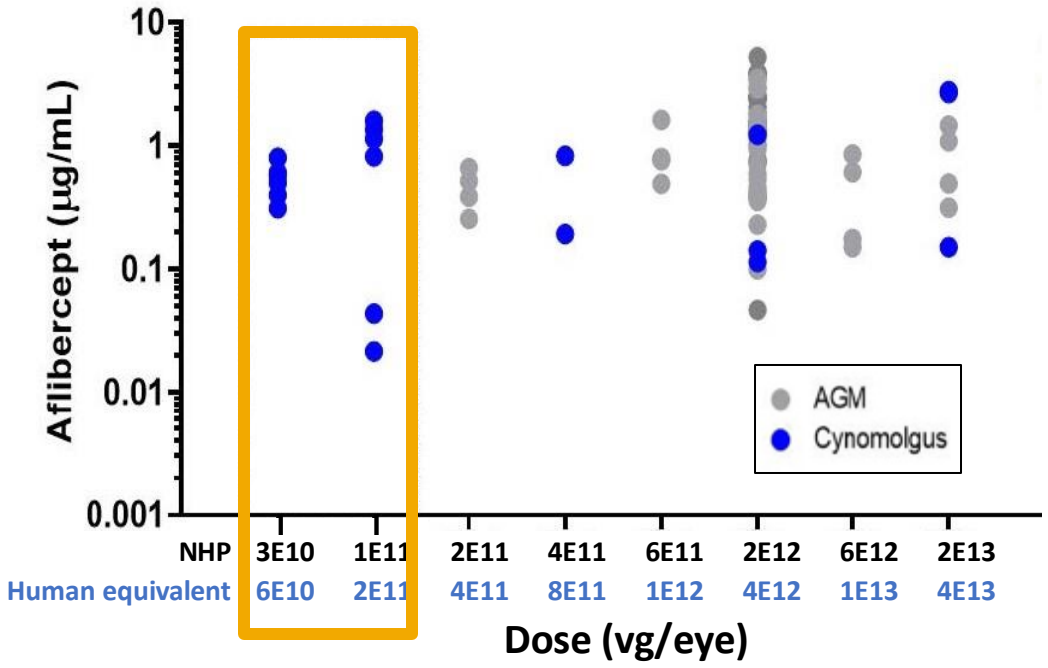
BCVA Δ: +13 letters
CST Δ: -135 µm

Anti-VEGF injection Study visit, no supplemental injection Baseline

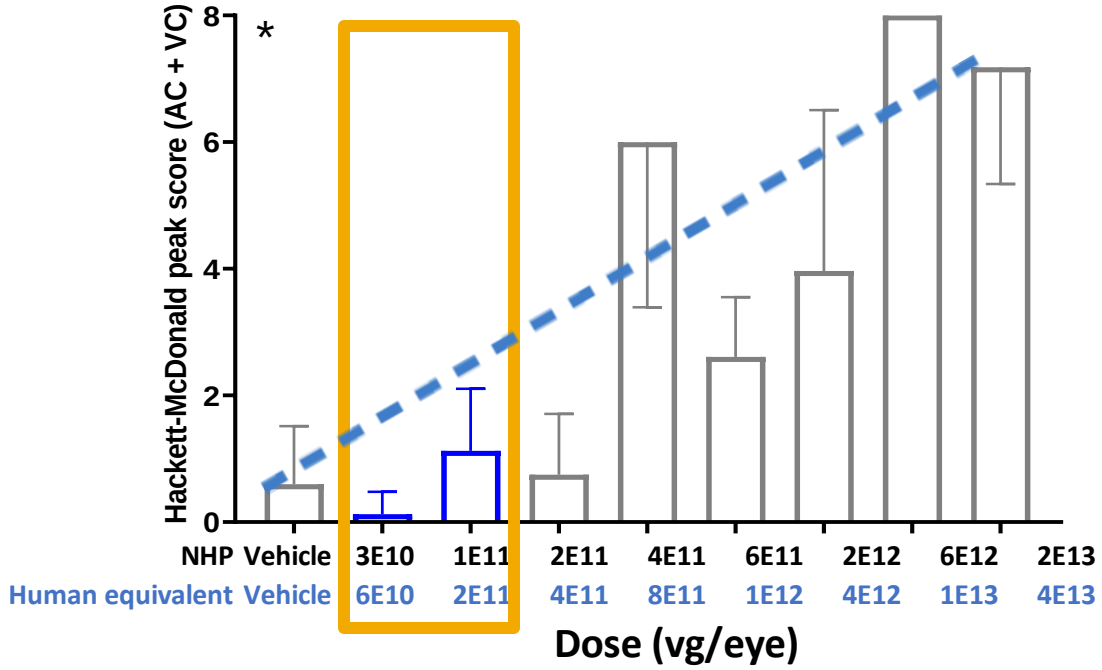
Data cut: 23Aug2023

- **NHP data demonstrate a flat dose response for aflibercept levels across 3 Logs**
- **NHP data shows improved IOI scores with lower doses (not prophylaxis)**

Aqueous Humor Aflibercept Levels



Inflammation Scores



*Scale is cumulative of two parameters for maximum score of 8.

Human Equivalent Dose (HED) is approximately twice the corresponding NHP dose based on eye volume. E.g., 2E11 is the HED of 1E11 NHP dose.
NOAEL established at NHP dose of 1E11 vg/eye. LUNA clinical trial doses outlined in orange box.
Schaefer-Swale K. 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. Poster presented at ASGCT 2023

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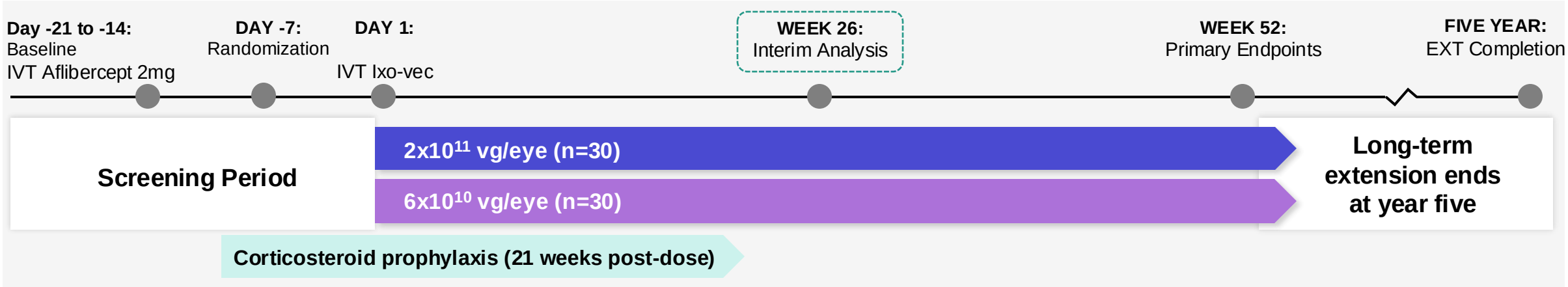
Multicenter, double-masked, randomized, parallel-group Phase 2 study

Key inclusion criteria:

- Responsive to anti-VEGF therapy; received a minimum of 2 injections for nAMD treatment
- Study eye BCVA (25 – 83 ETDRS letters)



Corticosteroid Prophylaxis

- Difluprednate 22 wks ± prednisone oral 10 wks
- Ozurdex IVT + difluprednate after week 4 ± prednisone oral 10 wks*
- Randomized 2:1 local versus local + oral

Supplemental Injection Criteria

- Increase in CST > 75 µm from BL confirmed by the CRC **OR**
- Loss of ≥ 10 letters in BCVA from BL due to new/worsening IRF or SRF **OR**
- New vision-threatening hemorrhage due to nAMD

*Study timeline and length of arrows depicted are not to scale. Baseline is defined as the day screening aflibercept is administered. *Protocol amended early in study to include difluprednate starting at week 4 to match the taper in difluprednate regimens; if initiated after week 4 visit, difluprednate may be adjusted at the discretion of investigator in consult with medical monitors (6 participants did not receive difluprednate as part of prophylaxis). BCVA, best corrected visual acuity; CST, central subfield thickness; BL, baseline; CRC, central reading center; IRF, intraretinal fluid; SRF, subretinal fluid*

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Demographics and Baseline Characteristics	LUNA 6E10 N = 30	LUNA 2E11 N = 30	LUNA Total N = 60	OPTIC Total N = 30
Mean age, years (SD)	75.4 (8.2)	77.7 (7.4)	76.6 (7.8)	79.0 (7.3)
Female, n (%)	16 (53%)	18 (60%)	34 (57%)	15 (50%)
Race, n (%) **White** **Asian**	 27 (90%) 2 (7%)	 28 (93%) 2 (7%)	 55 (92%) 4 (7%)	 30 (100%) 0
Mean years since nAMD diagnosis in the study eye (SD)	3.0 (2.9)	3.0 (3.1)	3.0 (2.9)	3.7 (2.8)
Mean annualized anti-VEGF injections in year prior to Day 1 (SD)	10.2 (1.7)	10.0 (3.3)	10.1 (2.6)	9.9 (1.9)
Mean BCVA, ETDRS letters (SD)	72.9 (8.8)	71.8 (6.4)	72.3 (7.7)	65.4 (7.2)
Mean CST, μm (SD)	360.6 (112.0)	340.5 (119.3)	350.6 (115.2)	397.0 (137.3)
Phakic lens status, n (%)	11 (37%)	11 (37%)	22 (37%)	10 (33.3%)

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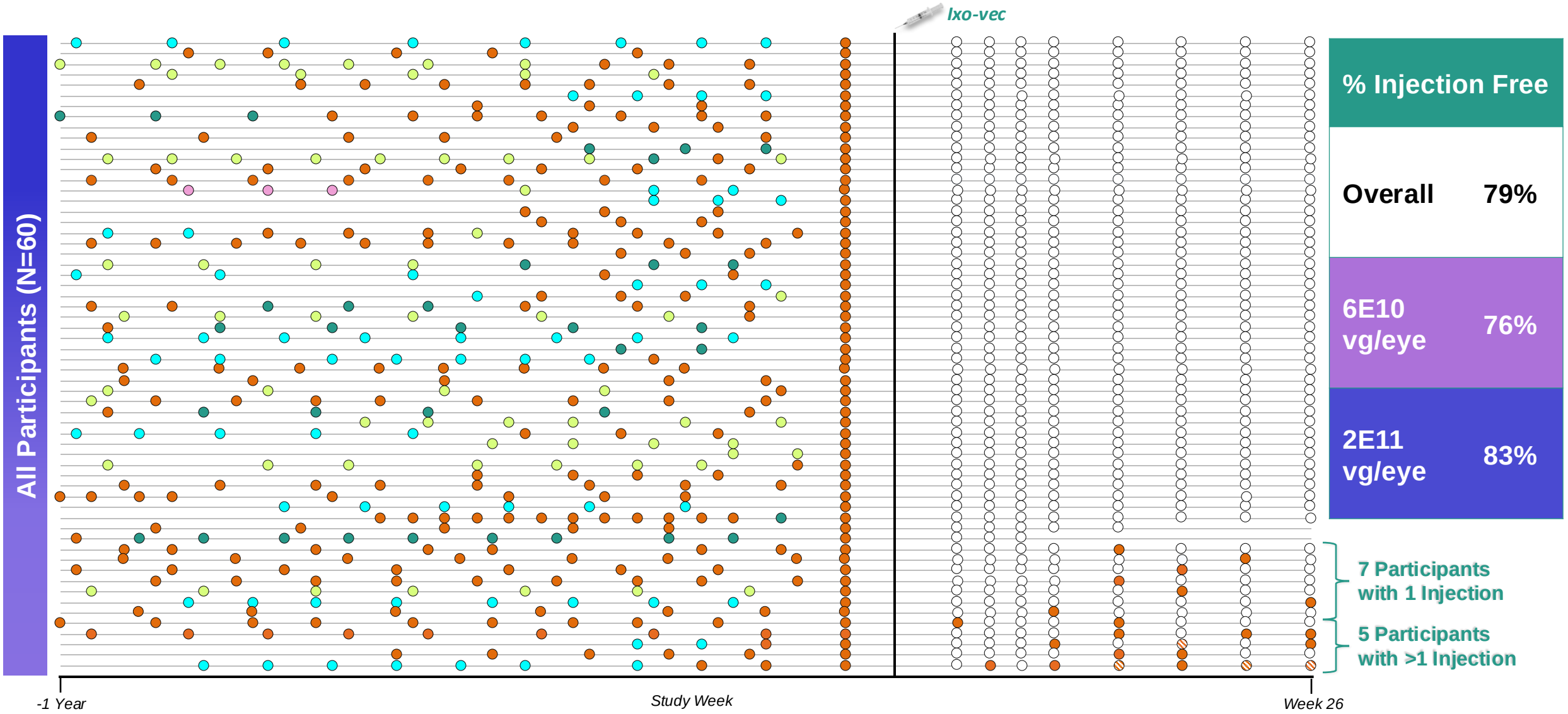

Doses pooled in swim lane plot to preserve investigator masking in an ongoing double masked study.

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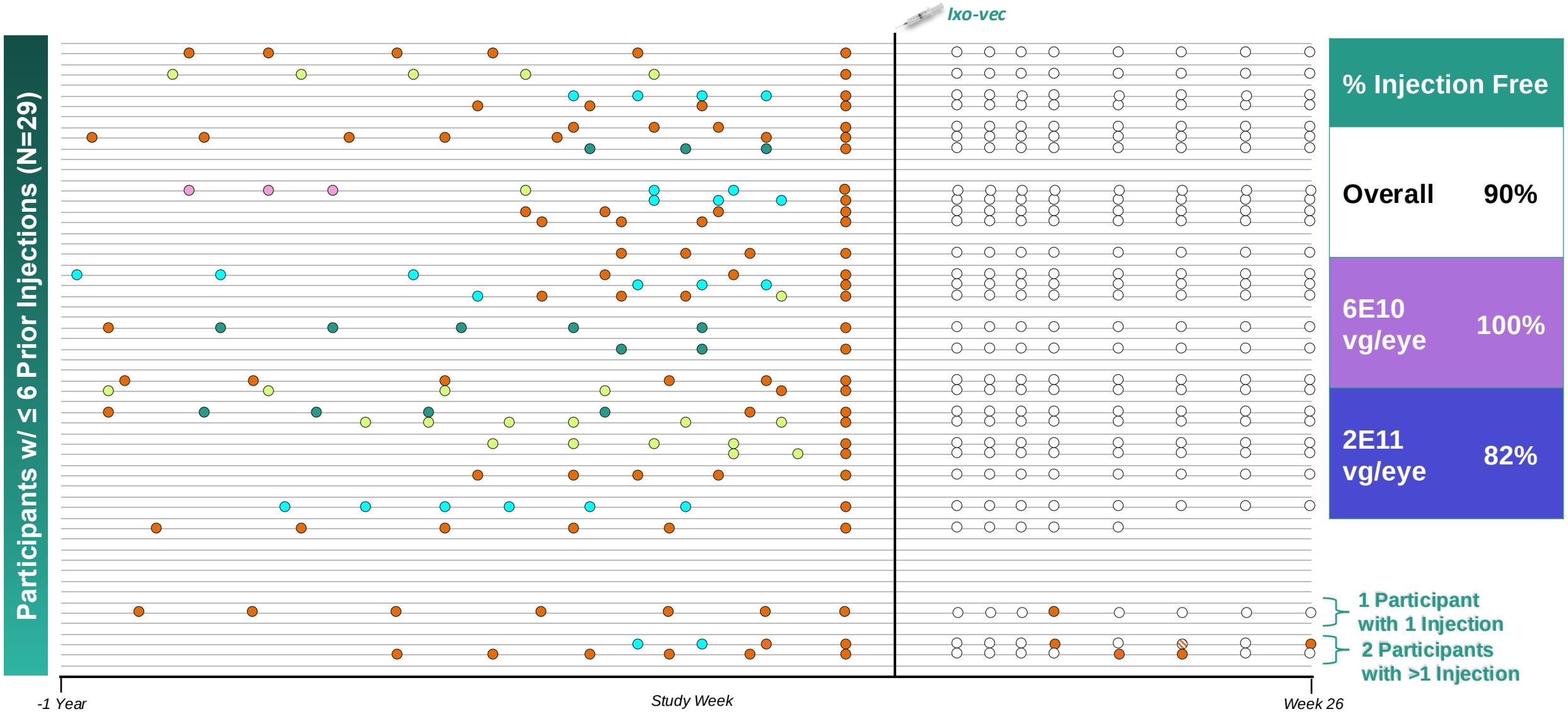

Patients received up to 6 injections in the year prior to entering the LUNA study excluding the LUNA aflibercept screening dose: 4.3 mean actual injections in both 6E10 and 2E11 dose cohorts and 10.2 and 9.5 mean annualized injections in 6E10 and 2E11 dose cohorts, respectively; 6E10: N=12, 2E11: N=17. Doses pooled in swim lane plot to preserve investigator masking in an ongoing double masked study.

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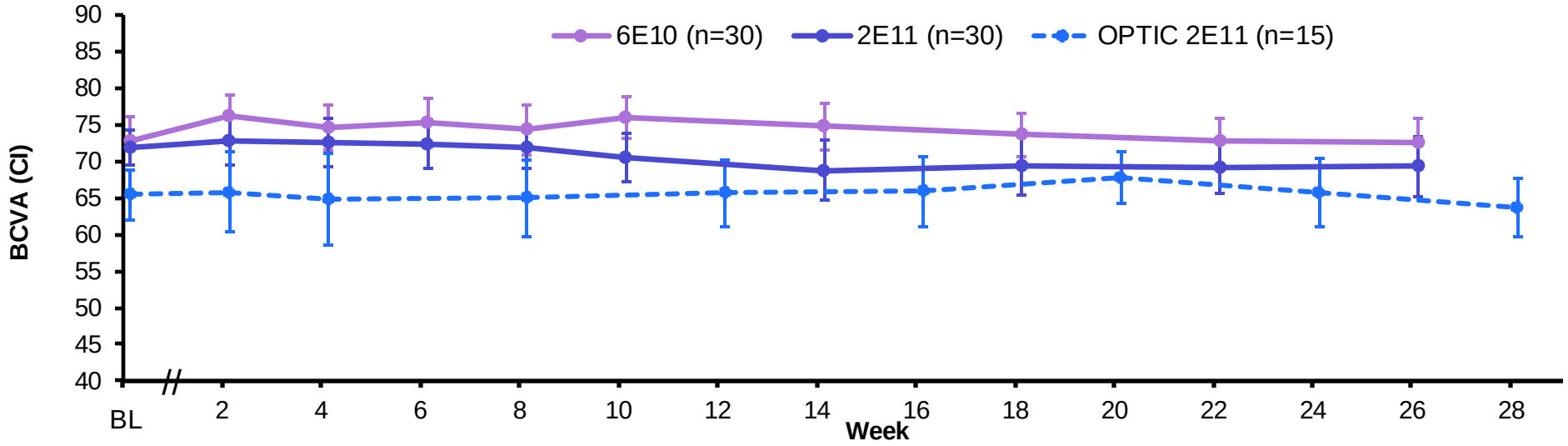
Data cut: 14Feb2024

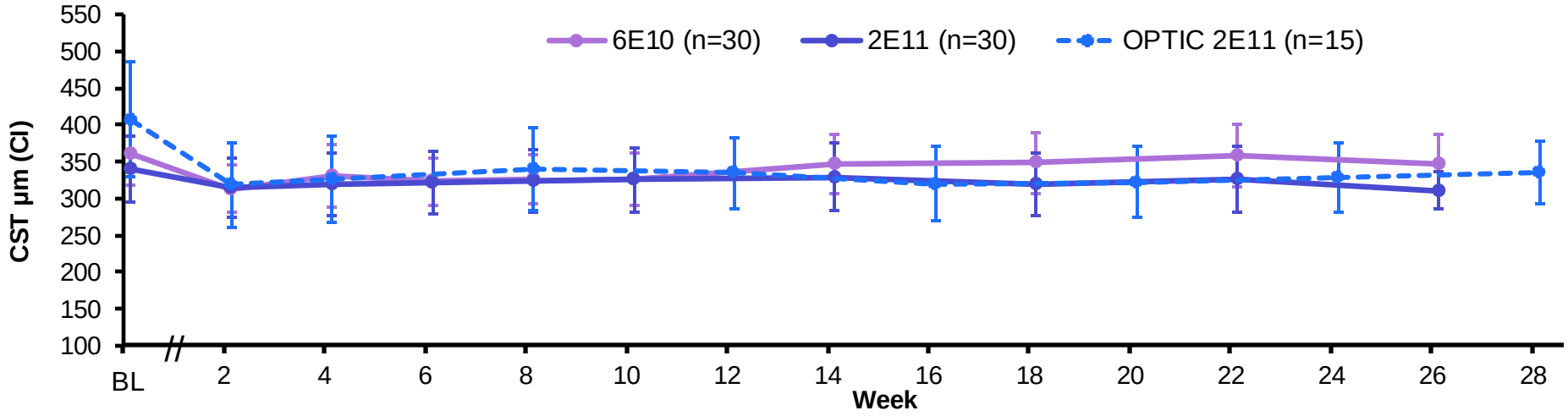
Mean Best Corrected Visual Acuity (BCVA) Over Time by Dose



LS Means BCVA Change from Baseline at Week 26, letters (CI)

- **-1.1 (-3.5, 1.2) 6E10 vg/eye**
- **-2.2 (-4.5, 0.2) 2E11 vg/eye**
- **-1.8 (-5.8, 2.2) 2E11 vg/eye OPTIC**

Mean Central Subfield Thickness (CST) Over Time by Dose



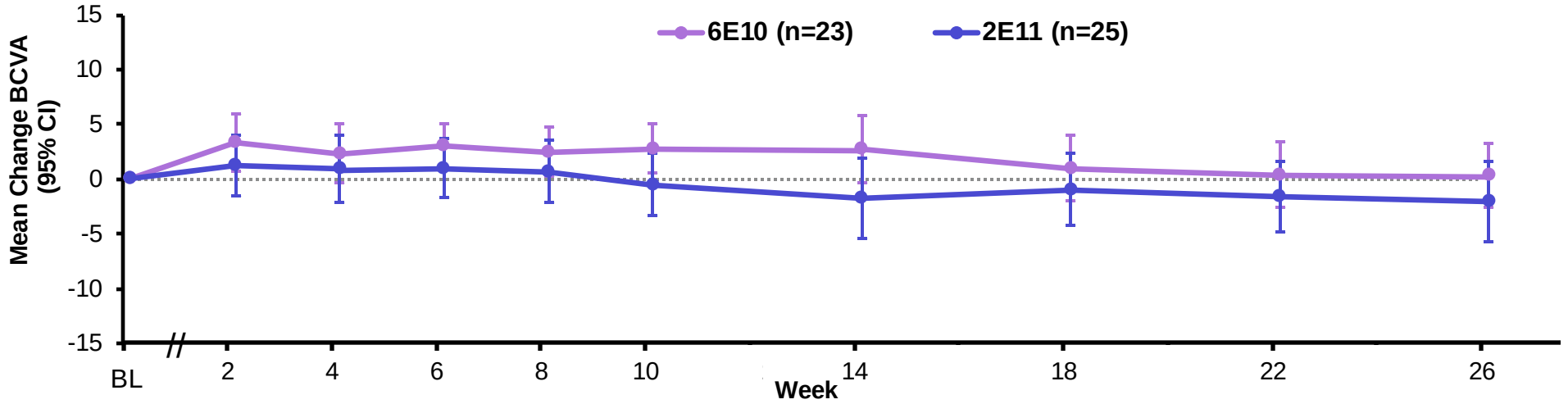
LS Means CST Change from Baseline at Week 26, µm (CI)

- **-12.6 (-30.2, 5.0) 6E10 vg/eye**
- **-12.0 (-30.0, 6.0) 2E11 vg/eye**
- **-71.1 (-130.8, -11.5) 2E11 vg/eye OPTIC**

*LUNA 95% CI; OPTIC 90% CI. LUNA and OPTIC differ in study visit cadence. LUNA: Least Squares Means change in BCVA and CST shown (based on Mixed Model Repeated Measures [MMRM] including dose group, baseline value, visit and visit*dose group). OPTIC: Mean change in BCVA and CST shown*

Data cut: 14Feb2024

Mean Change in BCVA Over Time in Supplemental Injection Free Participants, by Dose

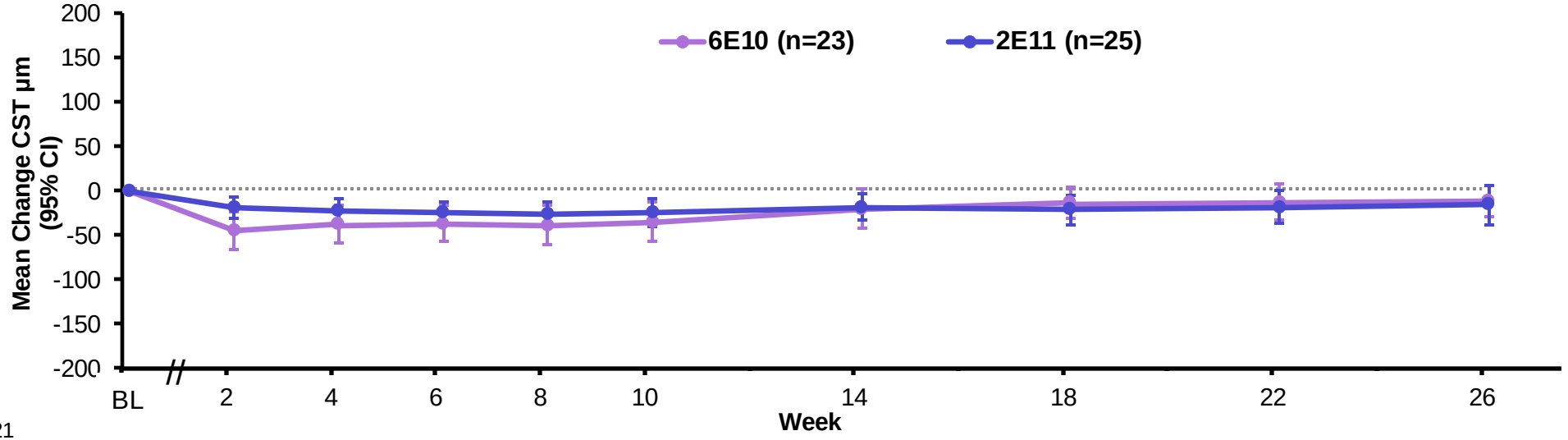


Mean BCVA Change from Baseline at Week 26, Letters (95% CI)

+0.3 (-2.6, 3.2) 6E10 vg/eye

-2.1 (-5.8, 1.6) 2E11 vg/eye

Mean Change in CST Over Time in Supplemental Injection Free Participants, by Dose



Mean CST Change from Baseline at Week 26, µm (95% CI)

-11.4 (-29.2, 6.4) 6E10 vg/eye

-15.9 (-38.4, 6.6) 2E11 vg/eye

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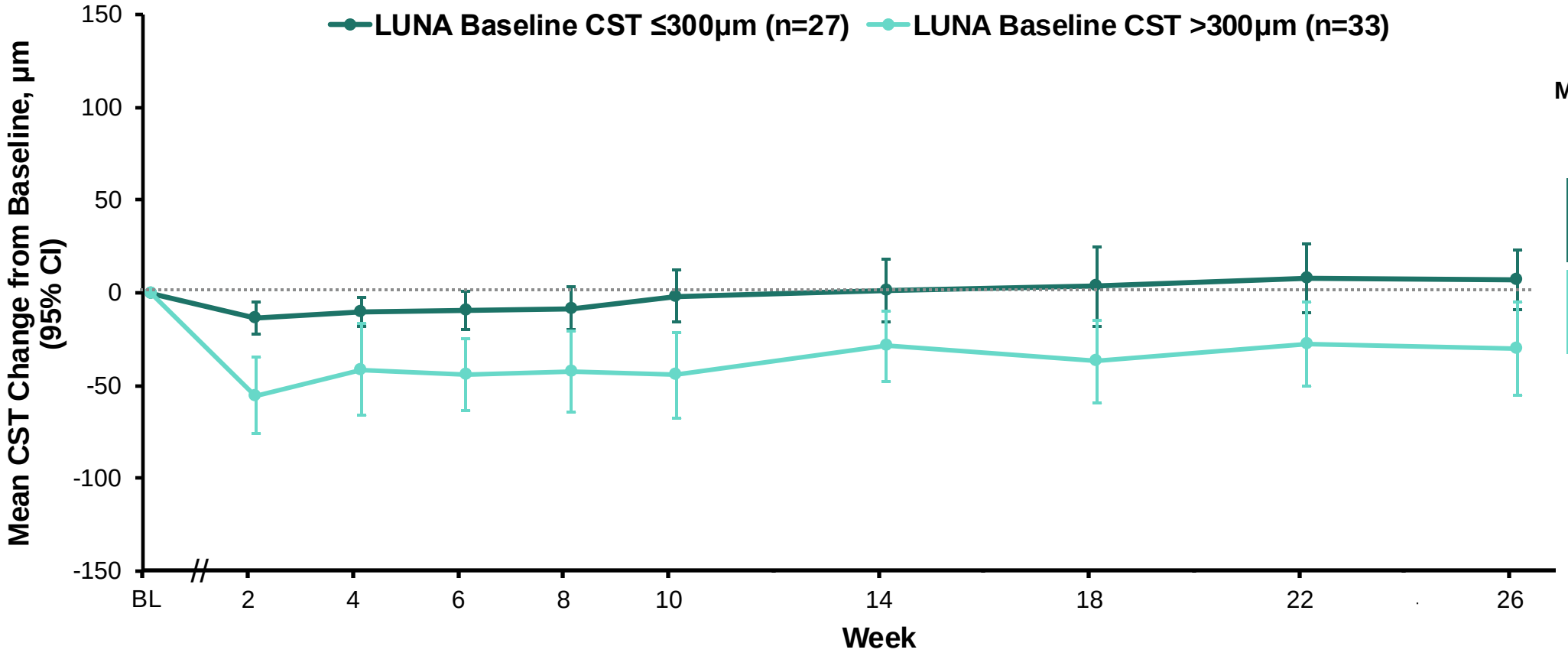
Data cut: 14Feb2024



Mean CST Change from Baseline at Week 26, µm (95% CI)

7.4 (-8.6, 23.5)
BL ≤300 µm

-30.2 (-55.2, -5.1)
BL >300 µm

Baseline Characteristic for Subgroup	CST ≤300 µm	CST >300 µm
Mean CST, µm (SD)	269.9 (18.7)	416.6 (119.1)

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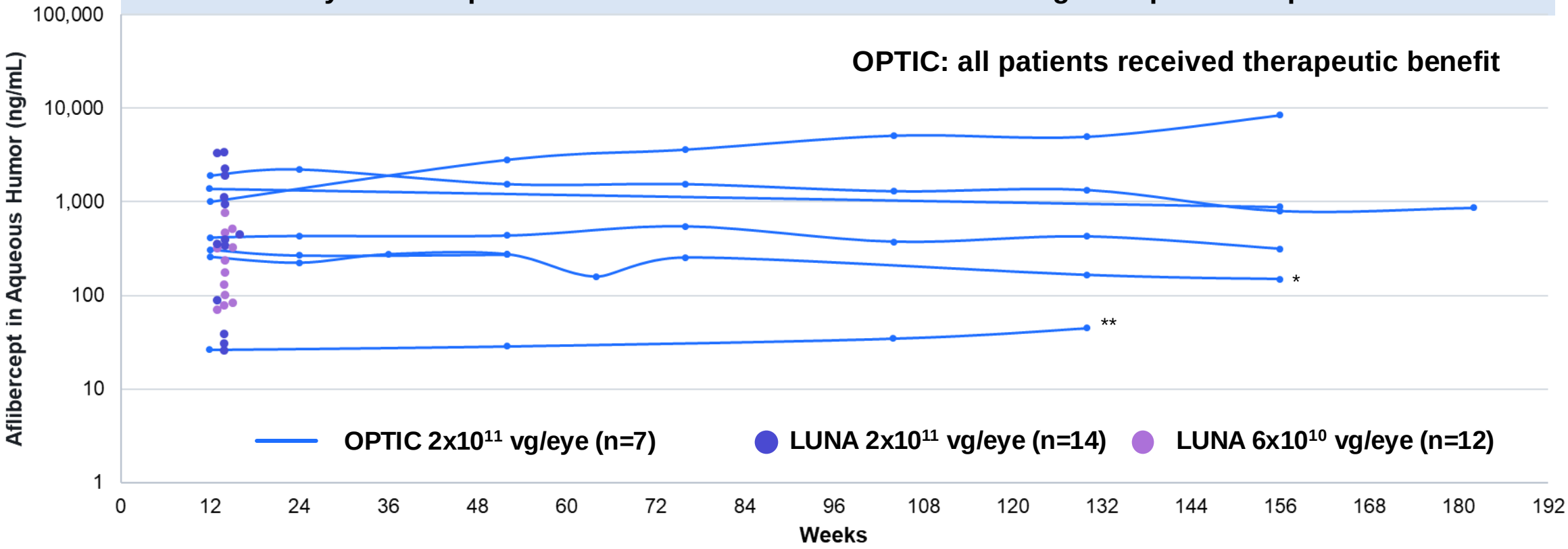
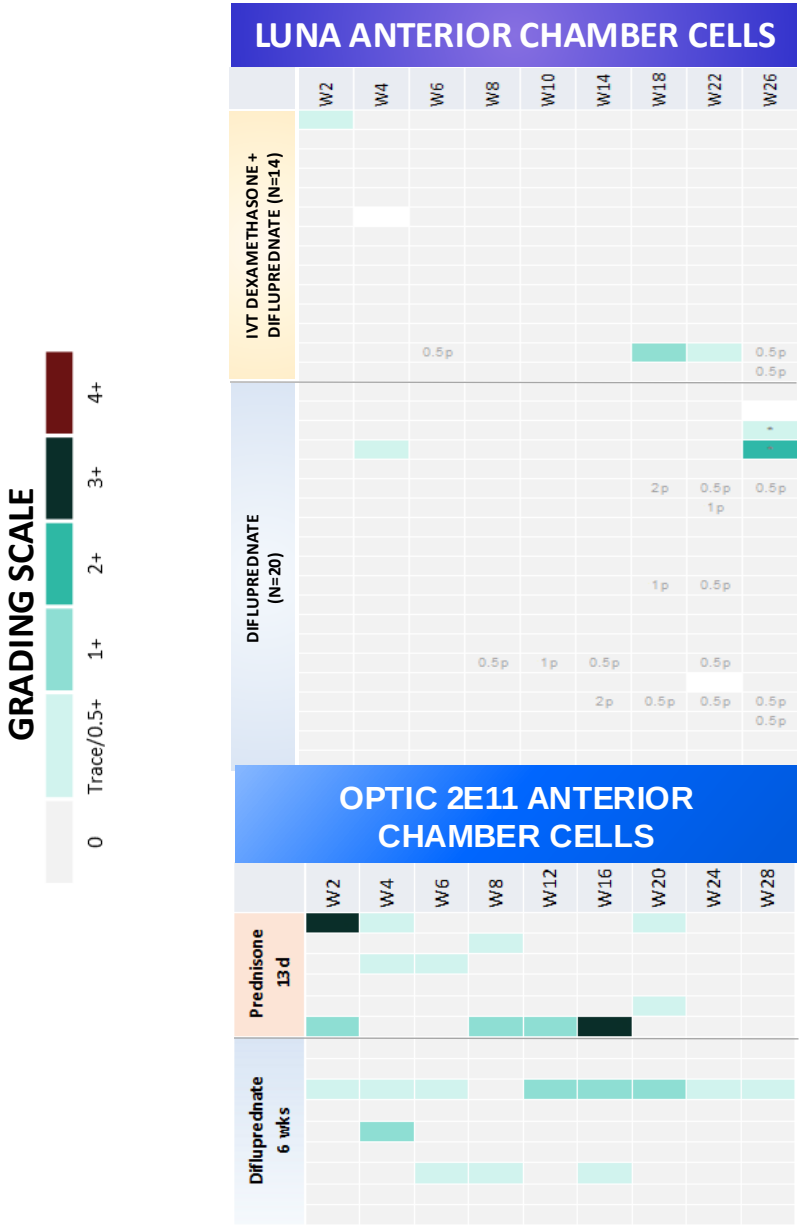
Data cut: 14Feb2024

Early aflibercept levels are associated with sustained long-term protein expression



No minimum aqueous humor aflibercept threshold for clinical benefit observed

*Data cuts: LUNA as of 15Nov2023, OPTIC as of 23Aug2023. LUNA Week 14 aflibercept levels plotted for 26 of 30 individual participants. 4 samples across both the 2E11 and 6E10 doses had aqueous aflibercept levels (ELISA assay BLOQ: <25 ng/ml). Of these, 2 were free of injections and 2 had either 1 or 2 supplemental injections through at least week 26. LUNA revised to stop collection of AH samples. *Participant received supplemental aflibercept injections at weeks 36, 52, 64, 68, 76, 80, 88, 92, 100, 130, 143, 156. 58% reduction in annualized anti-VEGF injections 3 years post-Ixo-vec compared to 12 months prior to Ixo-vec. **Participant received supplemental aflibercept injections at weeks 24, 64, 72, 80, and 156. 81% reduction in annualized anti-VEGF injections 3 years post-Ixo-vec compared to 12 months prior to Ixo-vec. At three timepoints (not indicated on plot), aflibercept levels were BLOQ.*



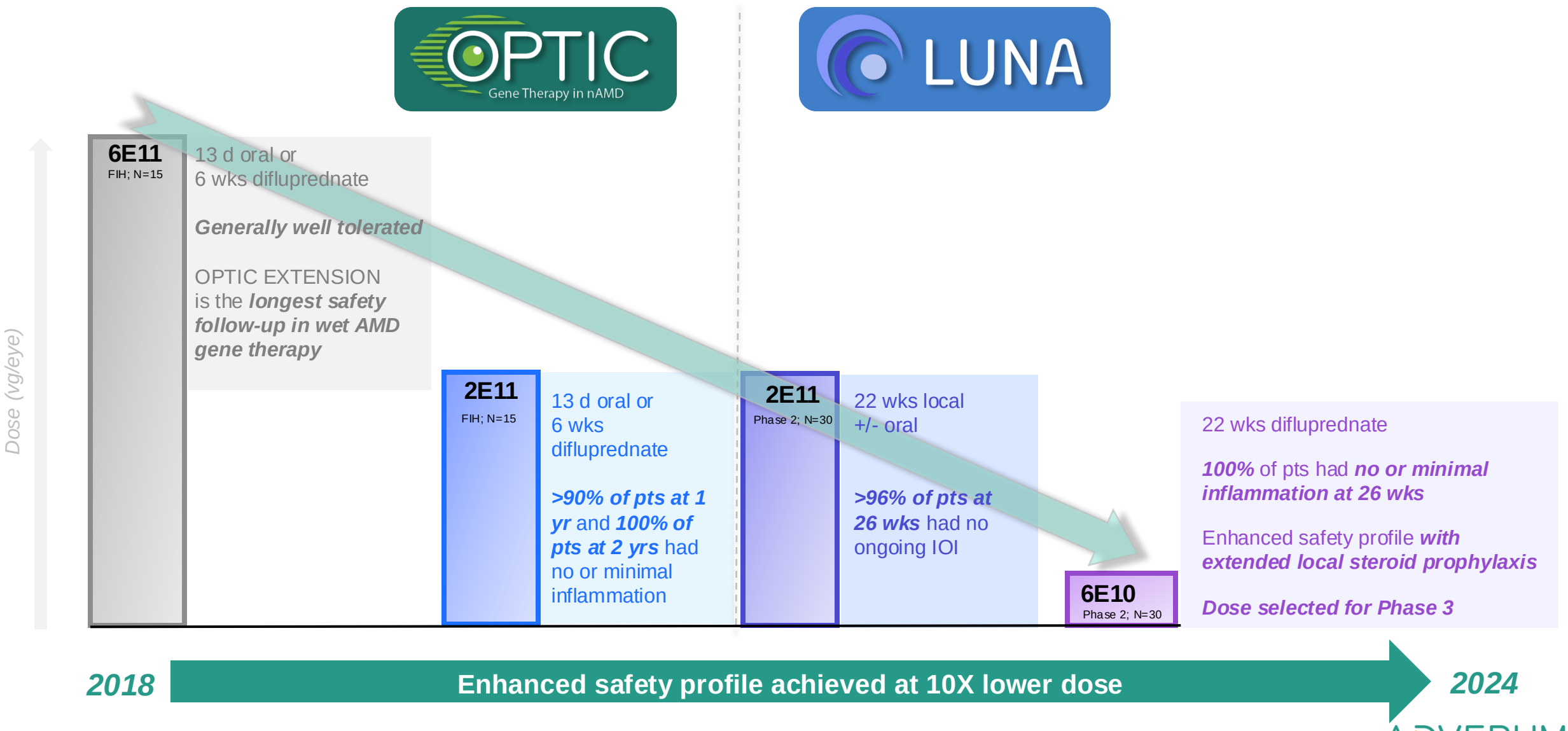
LUNA vs OPTIC Comparison

- In LUNA, an extended prophylaxis beyond OPTIC's 6-week topical regimen resulted in an improved inflammatory profile

- Local corticosteroid prophylaxis was effective in minimizing inflammation
  - **91% of participants had no or minimal inflammation** (0 or trace/0.5+ AC cells) **at any study visit through Week 26**
  - At Week 26, 0.5+ AC cells were present in 1 6E10 participant and 2+ in 1 2E11 participant

*Doses pooled in heatmaps to preserve investigator masking in an ongoing double masked study. *Mixed pigmented and non-pigmented cells are graded with the same color scheme and scale as non-pigmented cells. p, pigmented cell. AC, anterior chamber. V, vitreous. Cell grades as assessed by slit lamp; grade categories are based on the Standardization of Uveitis Nomenclature (SUN) and National Eye Institute Scores for white blood cells. No participant in the displayed arms had more than 2+.*

Data cut: 14Feb2024


OPTIC
Gene Therapy in nAMD
LUNA
Dose (vg/eye)
6E11
FIH; N=15
13 d oral or
6 wks diflupredn ate
Generally well tolerated
OPTIC EXTENSION
is the longest safety follow-up in wet AMD gene therapy
2E11
FIH; N=15
13 d oral or
6 wks
diflupredn ate
>90% of pts at 1 yr and 100% of pts at 2 yrs had no or minimal inflammation
2E11
Phase 2; N=30
22 wks local
+/- oral
>96% of pts at 26 wks had no ongoing IOI
6E10
Phase 2; N=30
22 wks diflupredn ate
100% of pts had no or minimal inflammation at 26 wks
Enhanced safety profile with extended local steroid prophylaxis
Dose selected for Phase 3
2018
Enhanced safety profile achieved at 10X lower dose
2024

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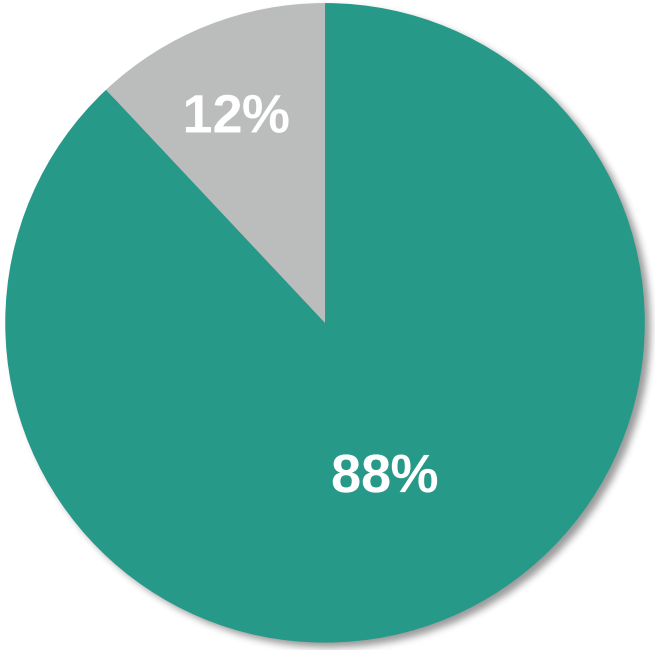
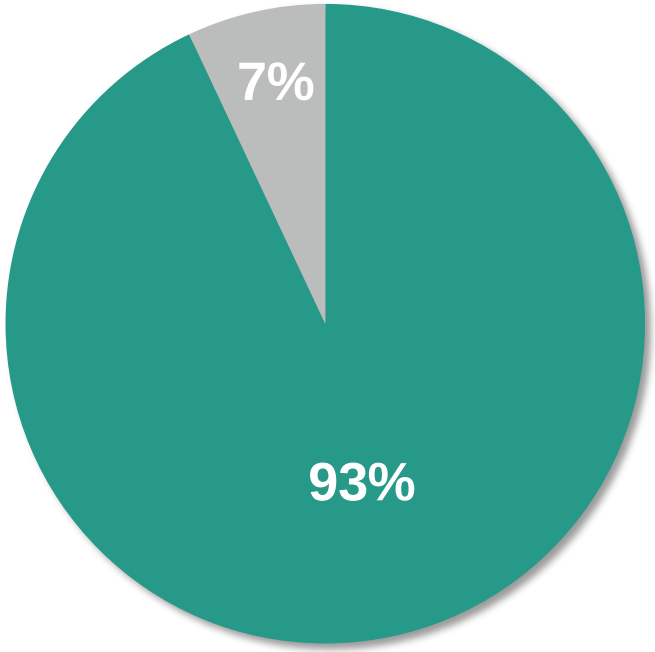
Would you prefer Ixo-vec therapy over the prior treatment(s) you received to treat your wet AMD?



N=57

Would you want to receive Ixo-vec therapy in your other eye if you had wet AMD in both eyes?



N=57

Yes No

100% of 6E10 + Difluprednate Participants (N=10) Prefer Ixo-vec Over Standard of Care Anti-VEGF

Based on a pre-specified Patient Preference Survey conducted by Adverum at week 26

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Key Takeaways

- **Industry Leading Proportion of Patients Injection Free:** 76% of hard-to-treat patients injection free
- **Treatment Burden Reduction:** 90% reduction in annualized injections
- **Visual and Anatomic Endpoints**: maintained through 26 weeks
- **Improved Safety Profile Compared to OPTIC:** with lower dose and enhanced prophylactic regimen
  - OPTIC 2E11 favorable long-term safety profile: 14 of 15 (93%) inflammation free at Y1, 100% at Y2
- **Strong Patient Preference for Ixo-vec over Standard of Care**
- **6E10 Selected for Phase 3 with Local Prophylaxis:** 10x safety margin

Anticipated Milestones

4Q'24:	**Continued Regulatory Interactions**
4Q'24:	**LUNA 52-Week Data, Including All Available Safety**
4Q'24:	**Phase 3 Pivotal Trial Design**
1H'25:	**Planned Phase 3 Start**

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