Ixo-vec (ixoberogene soroparvovec) Intravitreal Gene Therapy for Neovascular AMD: 3-Year Results from the Phase 1 OPTIC Extension Trial and Preliminary Data from the Phase 2 LUNA Trial

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– On behalf of the OPTIC and LUNA investigators –

AAO Retina Subspecialty Day • November 3-4, 2023

Disclosures

- Research Support-Wills Retina Service
  - 4DMT, **Adverum**, Allergan, Annexon, Apellis, Astellas, Eyepoint, Genentech, Graybug, Gyroscope, Iveric, Janssen, Kodiac, Lineage, NGM, Notal, Novartis, Ocugen, Opthea, Ocuterra, Regeneron, RegenXBio
- Consulting
  - 4DMT, **Adverum**, Alcon, Allergan, Annexon, Apellis, Clearside, Cognition, Eyepoint, Genentech, Graybug, Iveric, Janssen, Kodiac, Lineage, Merck, NGM, Novartis, Ocular Therapeutics, Ocugen, Ocuphire, Ocuterra, Ray, Regeneron, RegenXBio, Stealth, Thea, Zeiss

OPTIC EXT Study: 3-Year Long-term Safety and Efficacy of Ixo-vec for nAMD (5-Year Follow-up Total)

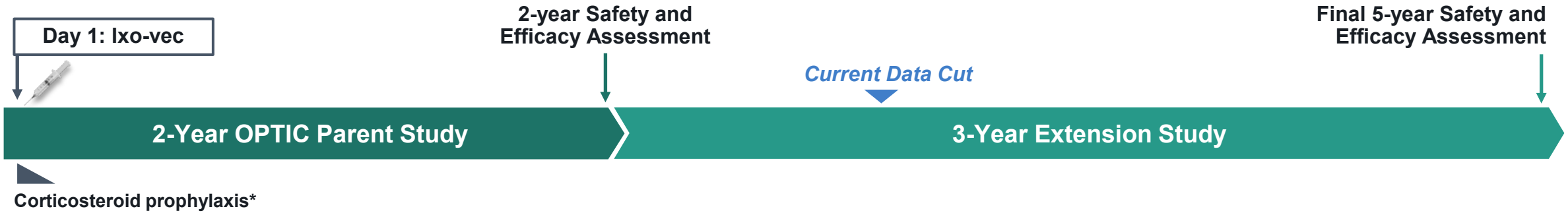
OPTIC Gene Therapy in nAMD

Primary Objective

Assess the long-term safety and tolerability of a single IVT injection of Ixo-vec

Secondary Objectives

- Evaluate vision maintenance (BCVA)
- Evaluate anatomy (SD-OCT)
- Assess the need for supplemental therapy



	Ixo-vec Dose	Corticosteroid Prophylaxis	Extension Scheduled Visits	Supplemental Aflibercept (2 mg IVT) Criteria:
Cohort 1 (n=6)	6 x 10^{11} high dose	Oral*, 13d	Regular quarterly assessments following completion of 2-year assessment in OPTIC parent study	• Loss of ≥10 letters in BCVA (ETDRS) from baseline that is attributed to IRF or SRF observed by the investigator • Increase in CST >75 µm from baseline • Presence of vision-threatening hemorrhage due to AMD • After initial supplemental injection in parent study, subsequent injections can be administered at investigator discretion
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		

*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.*

Ixo-vec OPTIC Study Baseline Characteristics

Baseline Characteristics	Cohort 1: $6x10^{11}$ OPTIC (N=6) OPTIC EXT (N=4)	Cohort 2: $2x10^{11}$ OPTIC (N=6) OPTIC EXT (N=4)	Cohort 3: $2x10^{11}$ OPTIC (N=9) OPTIC EXT (N=8)	Cohort 4: $6x10^{11}$ 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

Ixo-vec OPTIC EXT Study Safety Summary Through 3 Years Follow-up

Ixo-vec continues to be generally well tolerated through 3 years of follow-up

- No new ocular SAEs were reported
- No vasculitis, retinitis, choroiditis, vascular occlusions, or hypotony observed at either dose
- The most common adverse event was dose-dependent mild to moderate anterior inflammation (anterior chamber cells) responsive to topical corticosteroids
  - Three participants in the $2x10^{11}$ dose group and 3 participants in the $6x10^{11}$ dose group had ocular AEs deemed related to Ixo-vec in the extension study[1]
    - Only one participant in the $2x10^{11}$ dose group required topical corticosteroid treatment of inflammation in the extension study (for anterior chamber cells post cataract surgery)

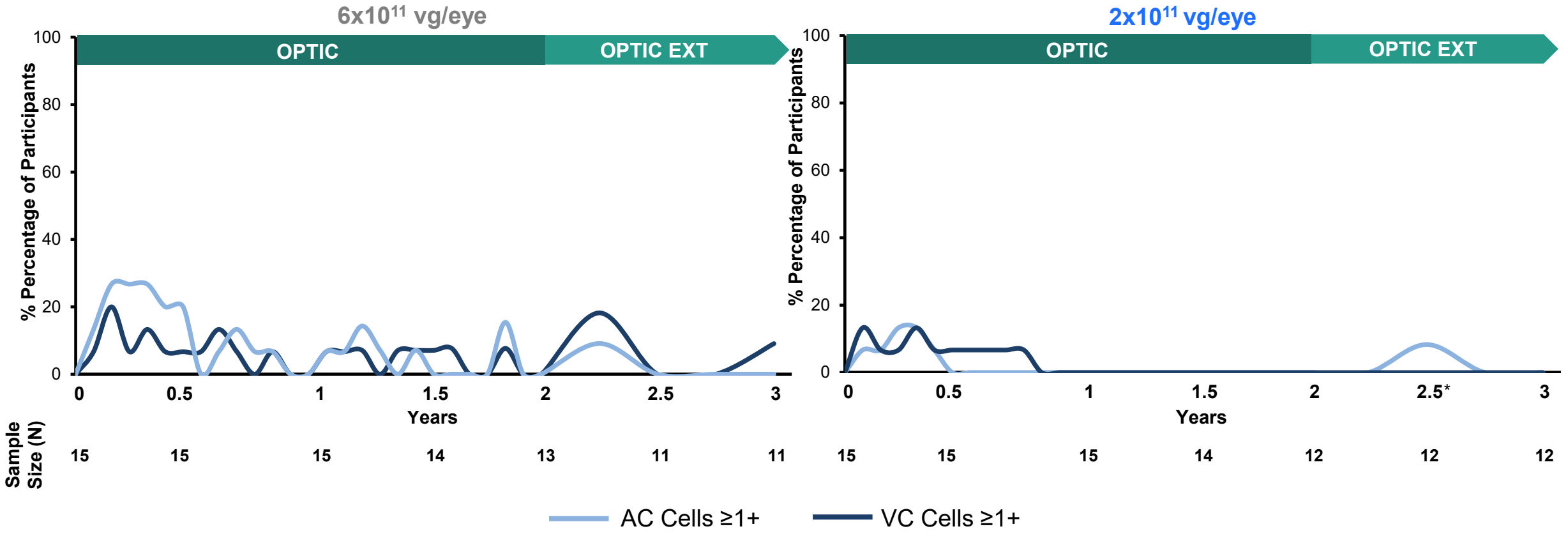
1. *Ocular AEs in $2x10^{11}$ dose group: anterior chamber cell, anterior chamber pigmentation, and iris adhesions and in $6x10^{11}$ dose group: anterior chamber cell and keratic precipitates*

AC, aqueous cells; AE, adverse event; SAE, serious adverse event; VC, vitreous cells; IOP, intraocular pressure.

Lower Immune Response with Ixo-vec 2x10^{11} vg/eye

OPTIC Gene Therapy in nAMD

Frequency of Inflammation Over Time by Dose



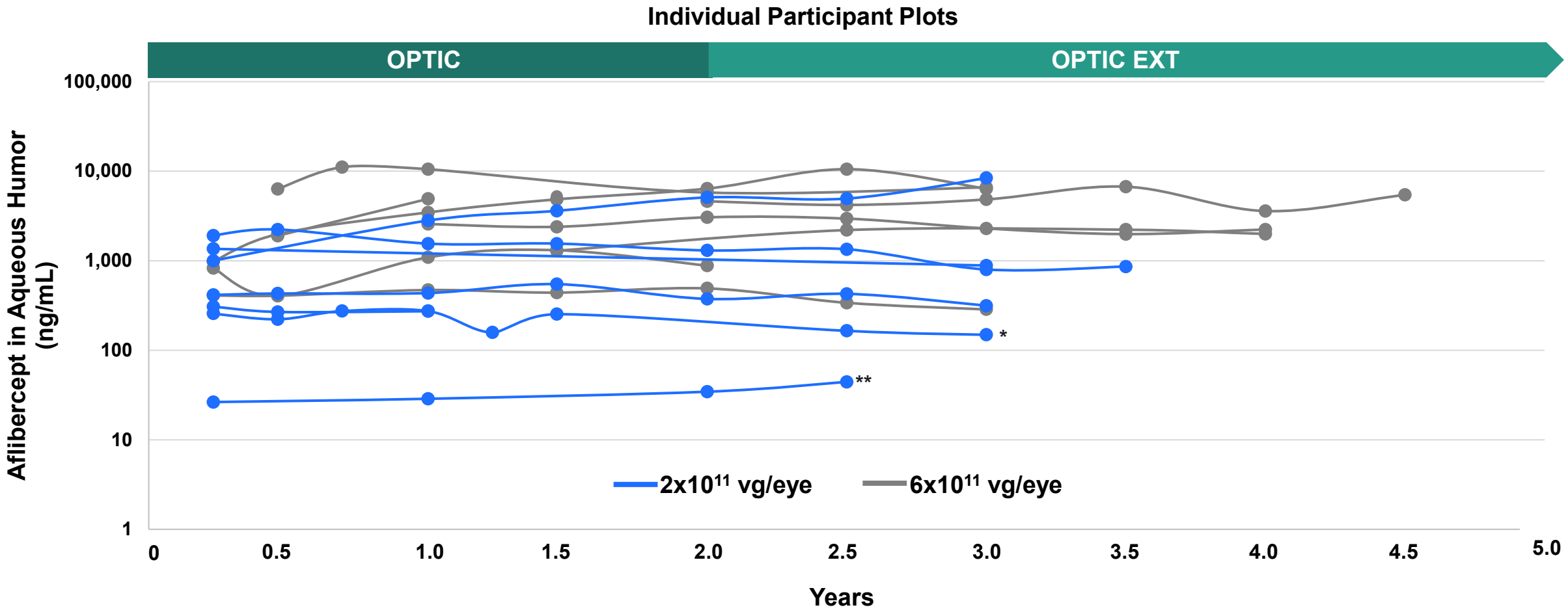
Corticosteroid prophylactic regimens in OPTIC parent study: 13 days oral prednisone or 6 weeks of topical drops

**2E11 Participant with inflammation at year 2.5 underwent a cataract surgery near the start of OPTIC EXT. At the next scheduled visit (3 months later—2.5 year visit), inflammation was detected that was responsive to topical corticosteroid. AC, aqueous cells; VC, vitreous cells. Cell grades as assessed by slit lamp, Grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria for aqueous cells and National Institutes of Health guidelines for vitreous cells. AC: 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 cells; VC: 0.5+: 1-10 cells 1+: 11-20 cells 2+: 21-30 cells 3+: 31-100 cells 4+: >100 cells; Rare cells are captured as 0.5+ for analysis*

Ixo-vec: Aqueous Aflibercept Levels Sustained Up to 4.5 Years

OPTIC Gene Therapy in nAMD

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



Protocol amendment for aqueous sample collection for participants that consented. To isolate the effect of Ixo-vec, samples that were collected within 2 months after supplemental aflibercept are not shown. Aqueous humor samples were collected prior to administration of supplemental aflibercept.

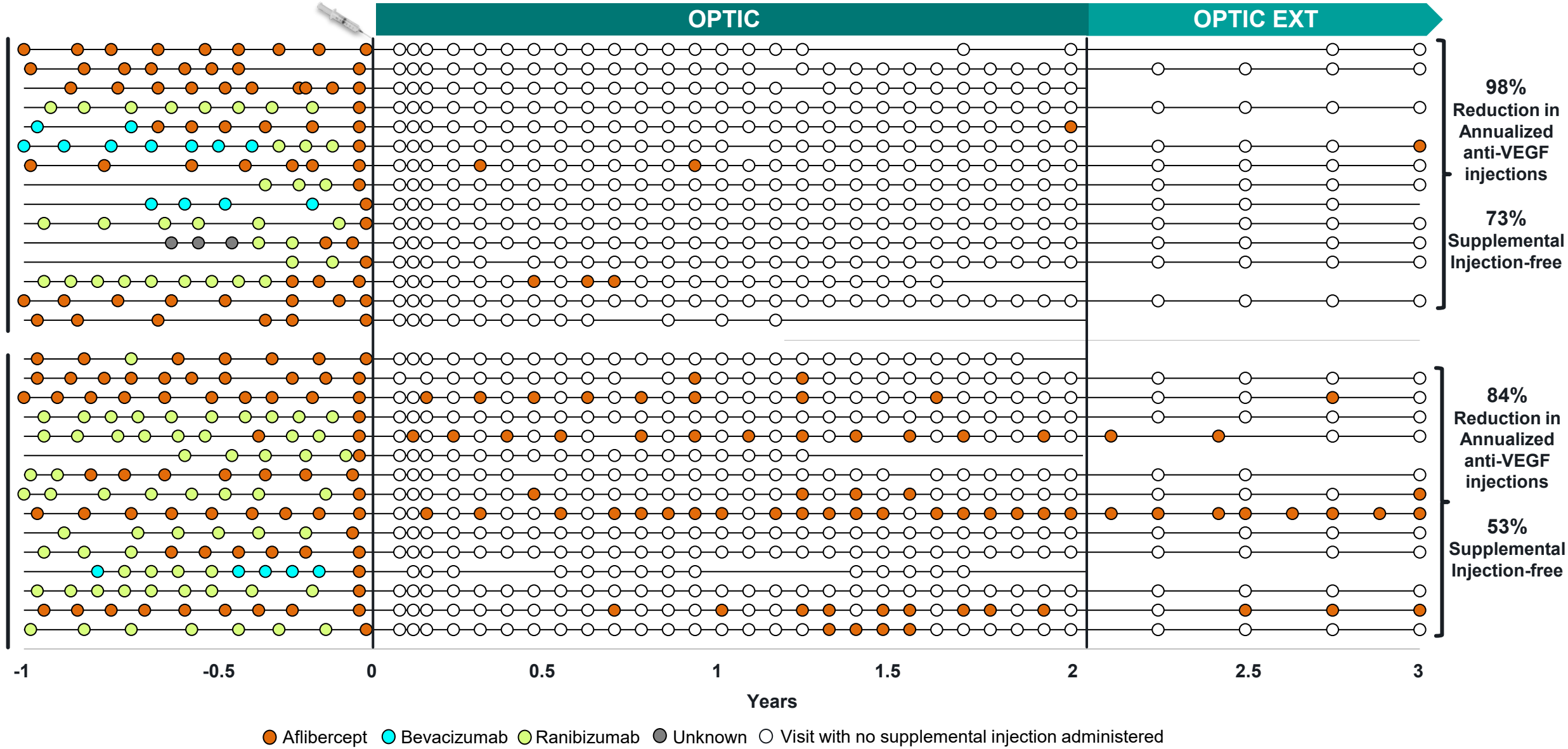
**Participant received supplemental aflibercept injections at weeks 36, 52, 64, 68, 76, 80, 88, 92, 100, 130, 143, 156. 58% reduction in annualized anti-VEGF injections 3 years post-Ixo-vec compared to 12 months prior to Ixo-vec.*

***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 below the level of quantification of the ELISA assay (25 ng/ml).*

Data cut: 23Aug2023

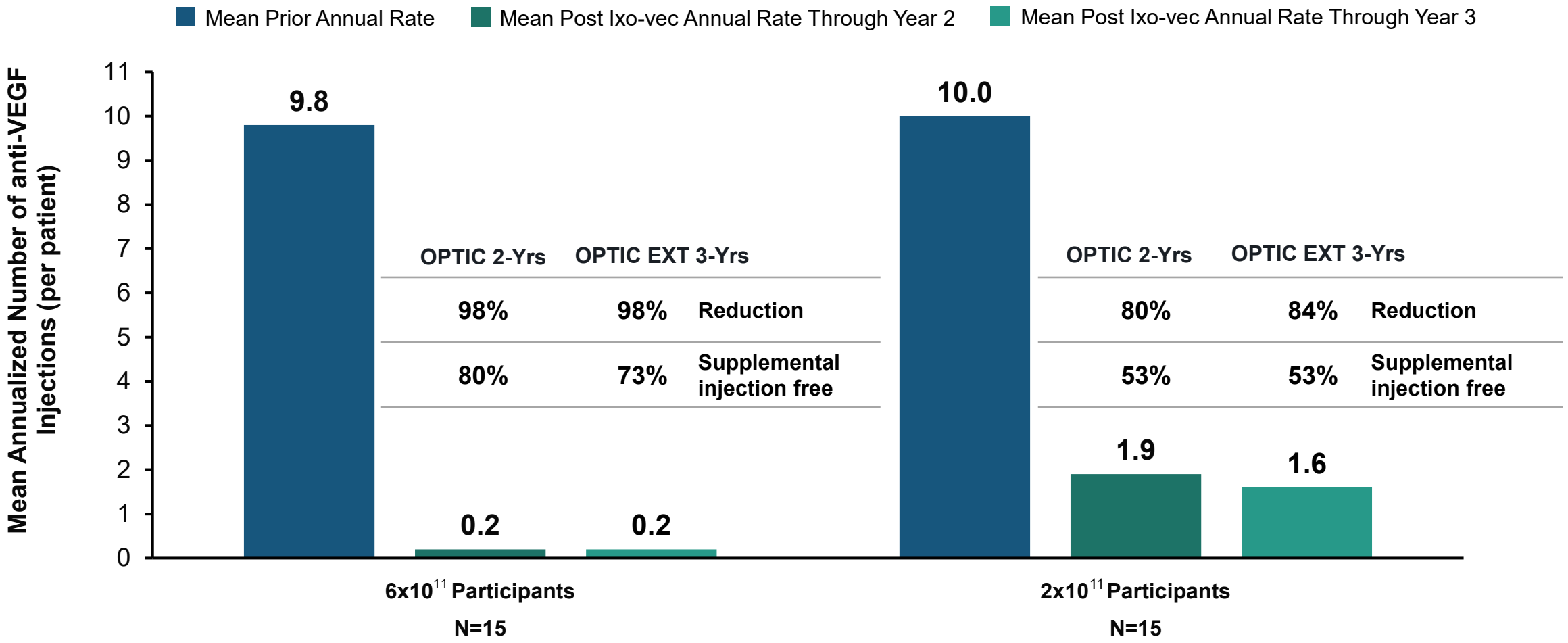
Reduction in Supplemental Aflibercept Injections Following Ixo-vec Sustained to 3 Years

OPTIC
Gene Therapy in nAMD



Supplemental aflibercept injections could be administered PRN after the first supplemental. Six patients were diagnosed <1 year prior to Ixo-vec 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

84-98% Reduction in Annualized Anti-VEGF Injections Following a Single Ixo-vec IVT Injection Through 3 Years

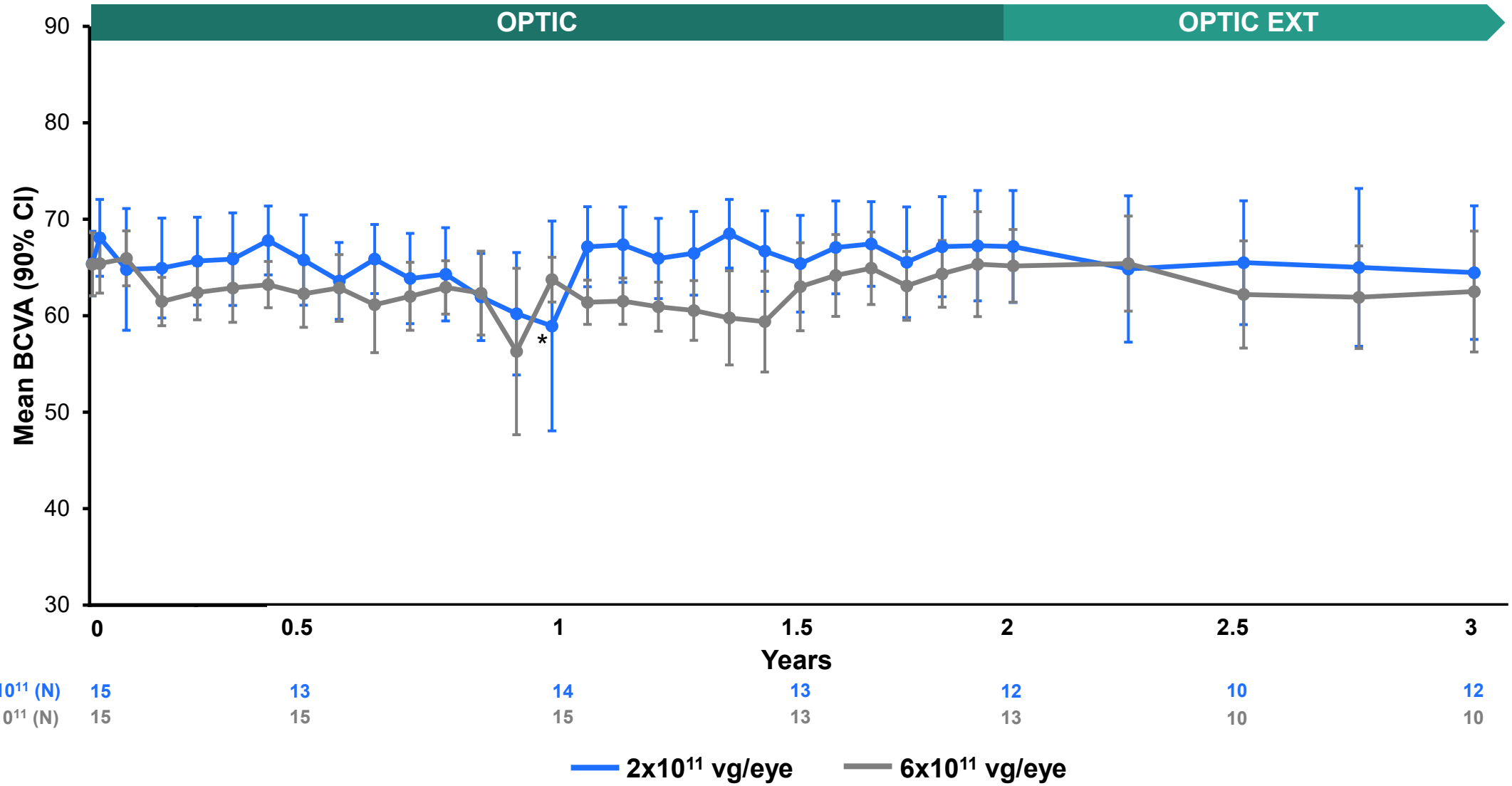


Annualized rate (Prior) = (number of IVTs in 12 months prior to Ixo-vec) / (days from the first IVT in the past 12 months to Ixo-vec / 365.25).
Annualized rate (Post) = (number of aflibercept IVTs since Ixo-vec) / (days from Ixo-vec to the last study follow-up / 365.25).
Analysis includes all participants from the OPTIC study.
VEGF, vascular endothelial growth factor.

BCVA Maintained Through 3 Years With Both Ixo-vec Doses

OPTIC
Gene Therapy in nAMD

Mean BCVA (90% CI) by Dose Over Time



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

-1.6 (-7.1, 3.9)
$2x10^{11}$ vg/eye

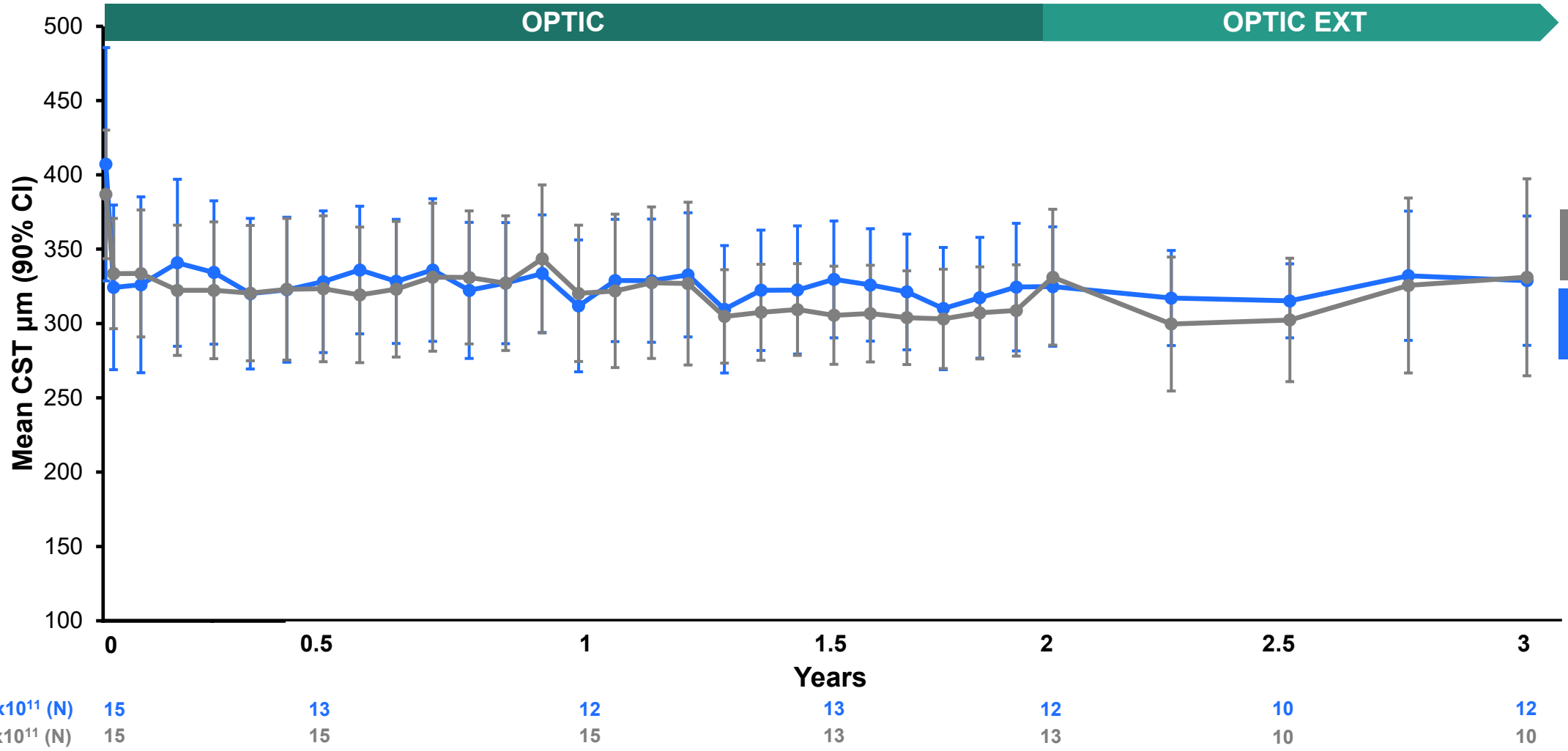
-2.4 (-6.4, 1.6)
$6x10^{11}$ vg/eye

**Cataract surgery*

Mean CST Reductions Maintained Through 3 Years With Both Ixo-vec Doses

OPTIC Gene Therapy in nAMD

Mean CST (90% CI) by Dose Over Time



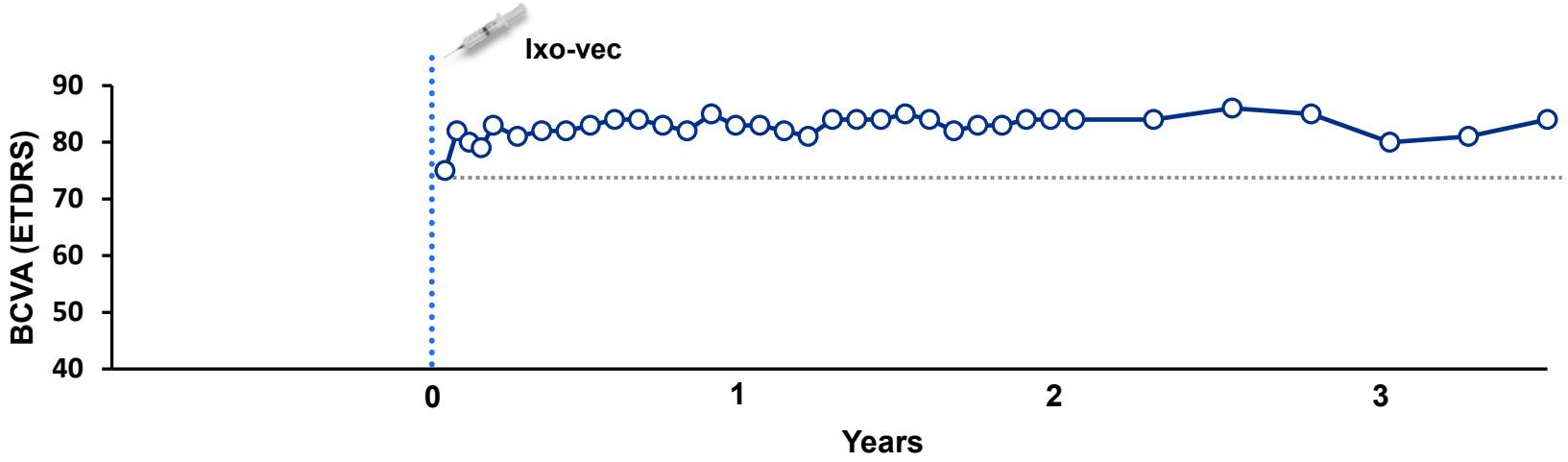
Mean CST (µm) change from baseline to last visit (90% CI)

-64.9 (-105.5, -24.2) $6x10^{11}$ vg/eye

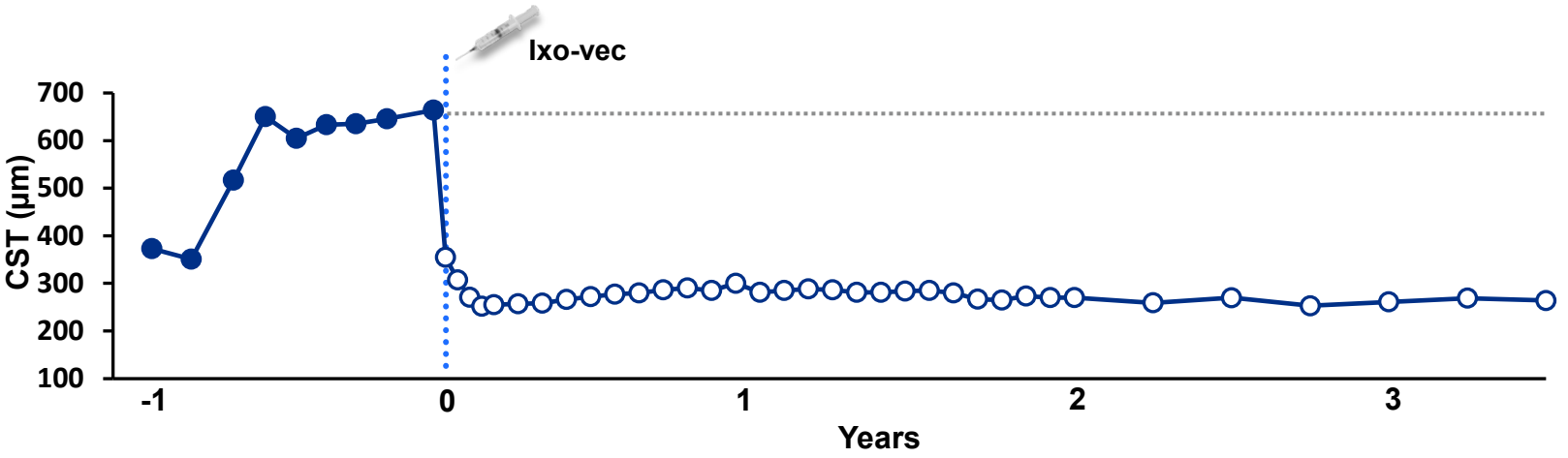
-89.7 (-164.0, -15.5) $2x10^{11}$ vg/eye

Ixo-vec 2x10^{11} vg/eye Case Study: 81-year-old Male With 19 IVTs Prior to Study and No Supplemental Anti-VEGF Over 3.5+ Years

OPTIC Gene Therapy in nAMD

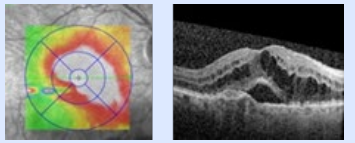


Aflibercept Q5W prior to Ixo-vec | 100% anti-VEGF injection free following Ixo-vec

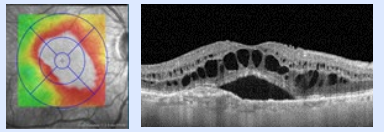


Anti-VEGF injection | Study visit, no supplemental injection | Baseline

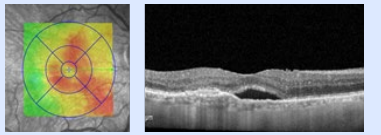
-30 weeks
Persistent fluid despite frequent anti-VEGF injections



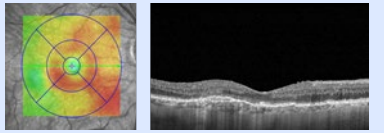
-2 wks (baseline)
BCVA: 75 letters
CST: 664 µm



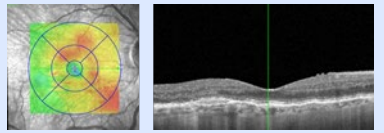
Day 0
Ixo-vec administration



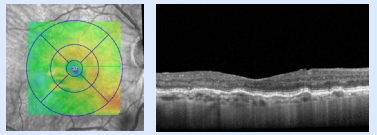
0.5 Years
BCVA Δ: +8 letters
CST Δ: -392 µm



1 Year
BCVA Δ: +8 letters
CST Δ: -383 µm



2 Years
BCVA Δ: +9 letters
CST Δ: -394 µm



3 Years
BCVA Δ: +5 letters
CST Δ: -403 µm

Historical BCVA data was not collected. Patient of Arshad Khanani, MD, MA, FASRS.

Ixo-vec OPTIC EXT Key Takeaways

- A single, in-office IVT injection of Ixo-vec provides long-term, durable clinical benefit for at least 3 years
  - Sustained therapeutic aflibercept expression up to 4.5 years
  - Mean annualized anti-VEGF injections were reduced by 84-98%, indicating substantial long-term treatment burden reduction
  - BCVA and CST were maintained or improved through 3 years with both doses
- Ixo-vec continues to be generally well tolerated through 3 years of follow-up
  - No new Ixo-vec related SAEs or any new safety findings were observed in the extension study
- The OPTIC EXT study will continue to follow enrolled participants for a total of 5 years

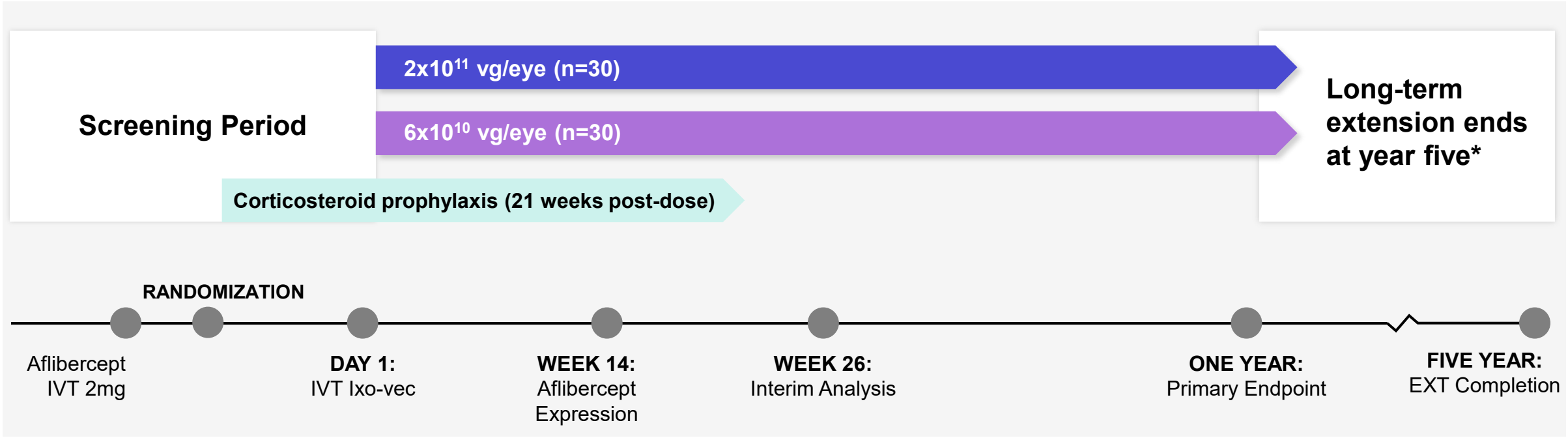
Ongoing LUNA Phase 2 in nAMD

Preliminary Results

Ongoing LUNA Phase 2 Trial in nAMD – Fully Enrolled

Study Description

- The LUNA trial is a multicenter, double-masked, randomized, parallel-group Phase 2 study
- Primary endpoints
  - Mean change in best corrected visual acuity (BCVA) from baseline to one year
  - Incidence and severity of adverse events
- 60 subjects have been enrolled and randomized equally between the $2x10^{11}$ vg/eye and $6x10^{10}$ vg/eye doses



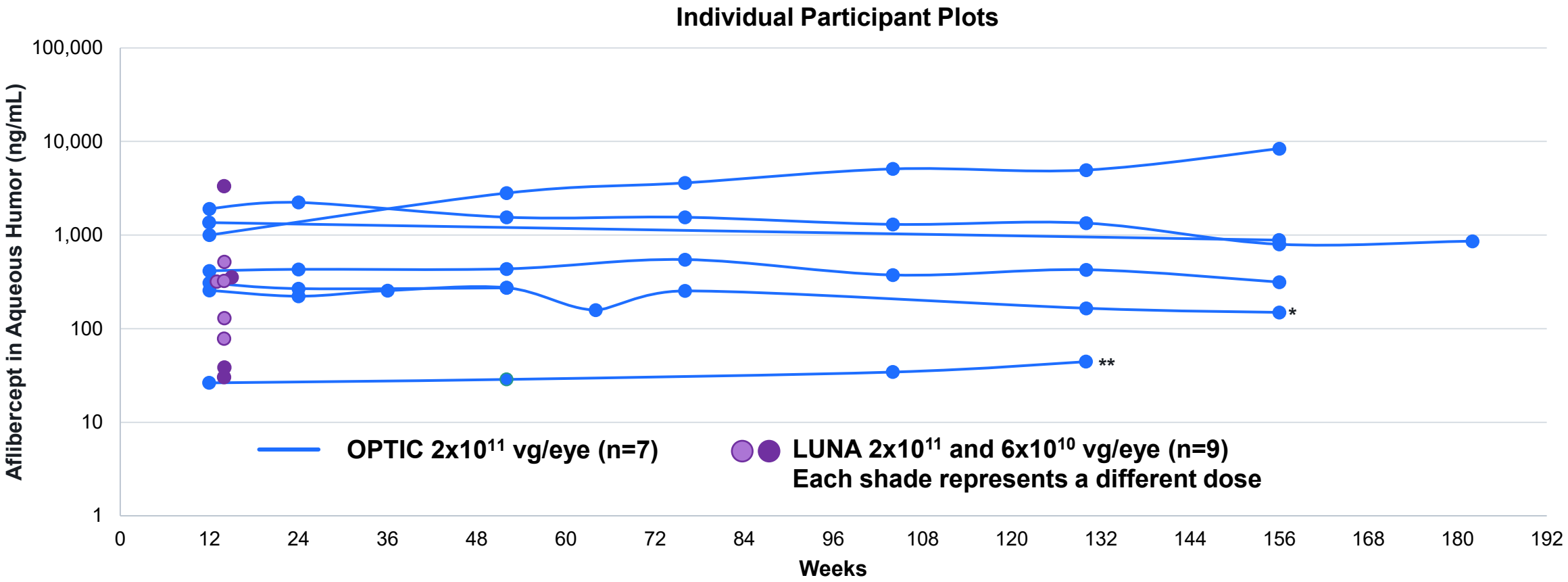
Study timeline and length of arrows depicted are not to scale

LUNA Demographics and Baseline Characteristics

Demographics and Baseline Characteristics	LUNA N = 60	OPTIC N = 30
Mean age, years (SD)	76.6 (7.8)	79.0 (7.3)
Female, n (%)	34 (57%)	15 (50%)
Race, n (%)		
White	55 (92%)	30 (100%)
Asian	4 (7%)	0
Mean years since nAMD diagnosis in the study eye (SD)	2.9 (3.0)	3.7 (2.8)
Mean annualized anti-VEGF injections in 12 months prior to Day 1 (SD)	9.9 (2.2)	9.9 (1.9)
Mean BCVA, ETDRS letters (SD)	72.3 (7.7)	65.4 (7.2)
Mean CST, μm (SD)	350.6 (115.2)	397.0 (137.3)
Phakic lens status, n (%)	22 (36.7%)	10 (33.3%)

LUNA Aqueous Humor Aflibercept Levels Within Therapeutic Range at Both Ixo-vec Doses

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



LUNA Week 14 aflibercept levels are plotted for 9 of 12 individual participants with quantifiable values. Three participants (including participants at both dose levels) had aflibercept levels below the level of quantification of the ELISA assay (25 ng/ml, not indicated on plot).
OPTIC protocol amendment for aqueous sample collection for participants that consented. To isolate the effect of Ixo-vec, samples that were collected within 2 months after supplemental aflibercept are not shown. Aqueous humor samples were collected prior to administration of supplemental aflibercept.
**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 below the level of quantification.*

Key Takeaways for Ixo-vec in nAMD

OPTIC – Long-term Extension

- A single, in-office IVT injection of Ixo-vec provides long-term, durable clinical benefit and substantial long-term treatment burden reduction for at least 3 years
    - Sustained therapeutic aflibercept expression up to 4.5 years; vision preserved with sustained improvements in anatomical outcomes through 3 years; and 84-98% reduction in annualized anti-VEGF injections
        - 53-73% of OPTIC participants remain supplemental injection free in year 3
- Ixo-vec continues to be generally well tolerated through 3 years

LUNA Phase 2

- The ongoing LUNA trial is fully enrolled and will further expand on the results from OPTIC in evaluating the efficacy and safety of a single, in-office IVT injection of Ixo-vec $2x10^{11}$ vg/eye and a new lower dose of $6x10^{10}$ vg/eye, combined with enhanced corticosteroid prophylaxis regimens, for the treatment of nAMD
- The preliminary results of LUNA indicate that by 14-weeks after a single IVT administration, both the $2x10^{11}$ and $6x10^{10}$ vg/eye Ixo-vec doses deliver measurable aqueous humor aflibercept concentrations that are comparable and in the therapeutic range of sustained levels observed in OPTIC

Acknowledgements: Investigators, Study Teams, and Participants

Prema Abraham, MD

Sean Adrean, MD

Benjamin Bakall, MD, PhD

Mark Barakat, MD

David Boyer, MD

Brandon Busbee, MD

Jorge Calzada, MD

Nauman Chaudhry, MD

Carl Danzig, MD

Victor Gonzalez, MD

Amir Guerami, MD

Paul Hahn, MD, PhD

Vivienne Hau, MD, PhD

Michael Ip, MD

Atul Jain, MD

Cameron Javid, MD

Chirag Jhaveri, MD

Brian Joondeph, MD

Arshad Khanani, MD

Gregg Kokame, MD

Xihui Lin, MD

James Major, MD

Sunil Patel, MD, PhD

Dante Pieramici, MD

Carl Regillo, MD

Veeral Sheth, MD

Michael Singer, MD

Benjamin Thomas, MD

Eduardo Uchiyama, MD

John Wells III, MD

Jeremy Wolfe, MD

Charles Wykoff, MD, PhD

Steven Yeh, MD

Glenn Yiu, MD, PhD