Ixoberogene soroparvovec (Ixo-vec) Intravitreal Gene Therapy for Neovascular Age-Related Macular Degeneration: Preliminary Results from the Phase 2 LUNA Study

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– On behalf of the LUNA investigators –

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Disclosures

- **Consultant:** AbbVie, Adverum Biotechnologies, Alcon, Allergan, Amgen, Annexin, Annexon, Apellis Pharmaceuticals, Aviceda Therapeutics, Beacon Therapeutics Clearside Biomedical, Complement Therapeutics, 4DMT, Exegenesis, EyePoint Pharmaceuticals, Fronterra Therapeutics, Genentech, Gyroscope Therapeutics, i-Lumen Scientific, Iveric Bio, Janssen Pharmaceuticals, Kodiak Sciences, Kriya Therapeutics, Nanoscope, Novartis, Ocular Therapeutix, Oculis, Ocuphire, OcuTerra, Olive BioPharma, Opthea, Oxular, Oxurion, Perfuse, Ray Therapeutics, Recens Medical, Regeneron Pharmaceuticals, Regenxbio, Revive, RevOpsis, Roche, Sanofi, Stealth BioTherapeutics, Thea Pharma, Unity Biotechnology, Vanotech and Vial
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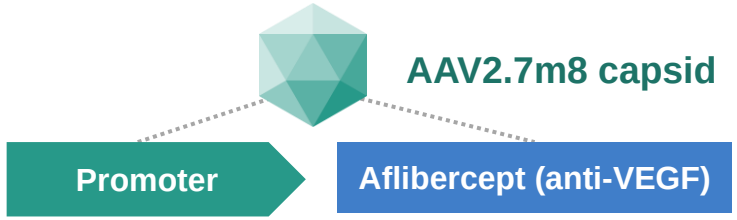
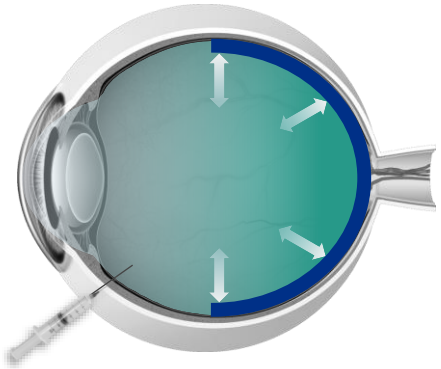
Ixo-vec IVT Gene Therapy is Designed to Provide Continuous Delivery of Aflibercept for Long-term nAMD Management and Preservation of Vision

AAV2.7m8 capsid engineered via directed evolution for enhanced transduction carrying a coding sequence for the anti-VEGF protein aflibercept



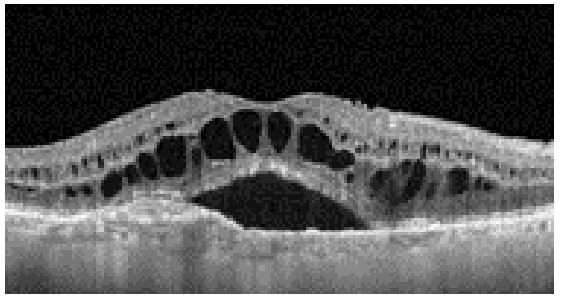
Following a one-time IVT Ixo-vec injection, transduced retinal cells become the source of continual aflibercept production



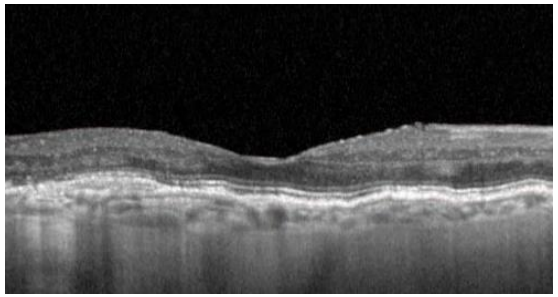
IVT injection of Ixo-vec

Long-term data from the FIH OPTIC study demonstrate sustained efficacy outcomes through 3 years

OPTIC 2x10^{11} vg/eye Participant with No Supplemental anti-VEGF Injections Through 3 Years



Baseline
BCVA (ETDRS): 75



Year 3
BCVA (ETDRS): 80

IVT: intravitreal; FIH: first-in-human

Grishanin, R, et.al. Molecular Ther 2019; 27(1), 118-129; Khanani AM et al. Lancet eClinical Medicine. 2024; Regillo CD. AAO Annual Meeting 2023. San Francisco, CA

LUNA Phase 2 Trial in Previously Treated Patients with nAMD

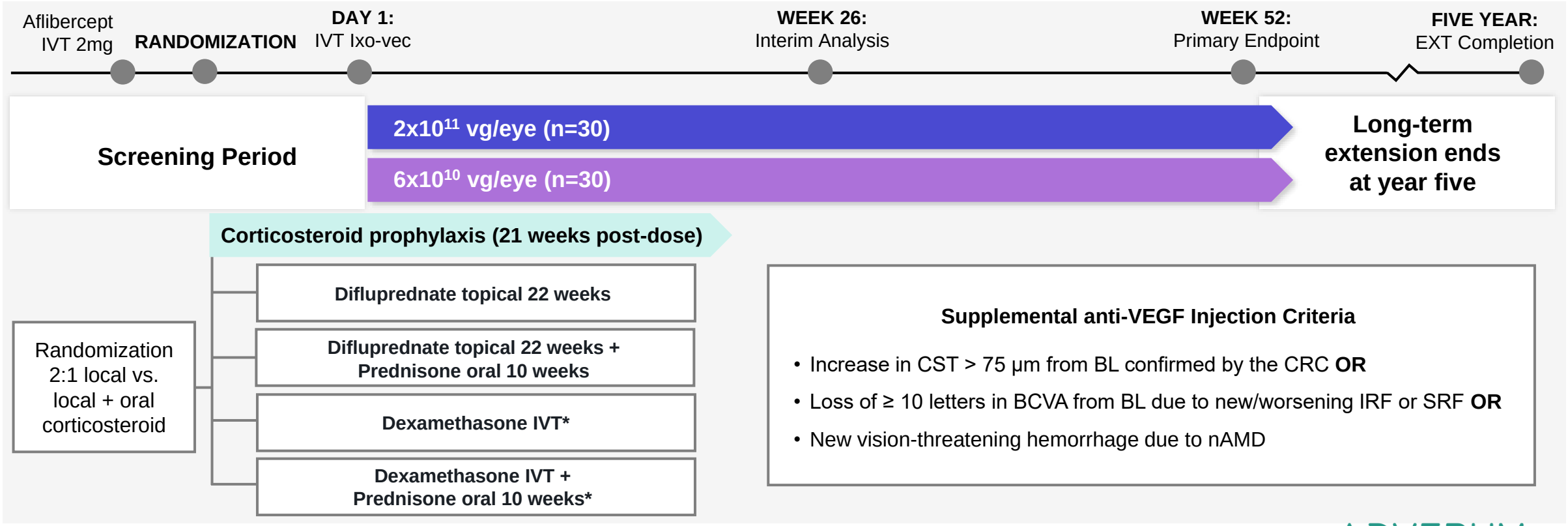
Multicenter, double-masked, randomized, parallel-group Phase 2 study

Key inclusion criteria

- Demonstrated response to anti-VEGF therapy and under active treatment for CNV due to nAMD (minimum of 2 injections within 4 months of entry)
- Study eye BCVA in the range of 25 – 83 ETDRS letters

Primary endpoints

- Mean change in BCVA from baseline to one year
- Incidence and severity of adverse events



*Study timeline and length of arrows depicted are not to scale; *Protocol amended early in study to include difluprednate after week 4 to match the taper in difluprednate regimens. BCVA: best corrected visual acuity; CST: central subfield thickness; BL: baseline; CRC: central reading center; IRF: intraretinal fluid; SRF: subretinal fluid*

LUNA Study Disposition

Participant Disposition	
Number of participants randomized and dosed with Ixo-vec	60
Number of participants who completed Week 14	54
Number of participants who completed Week 26	26
Number of participants who discontinued after Ixo-vec dosing	2
Reason for discontinuation (not related to Ixo-vec) • Death (Abdominal mesenteric mass, multiple organ failure, and septic shock – not related to study drug) • Adverse event (Dementia – not related to study drug)	 1 1
Mean follow-up duration in Weeks from Day 1	23.3

A prespecified interim analysis will be conducted when all participants complete their 26-week study visit

Safety outcomes, AH aflibercept levels, BCVA, and CST current through 15Nov2023. Supplemental anti-VEGF data current through 02Jan2024 due to data availability via IRT.

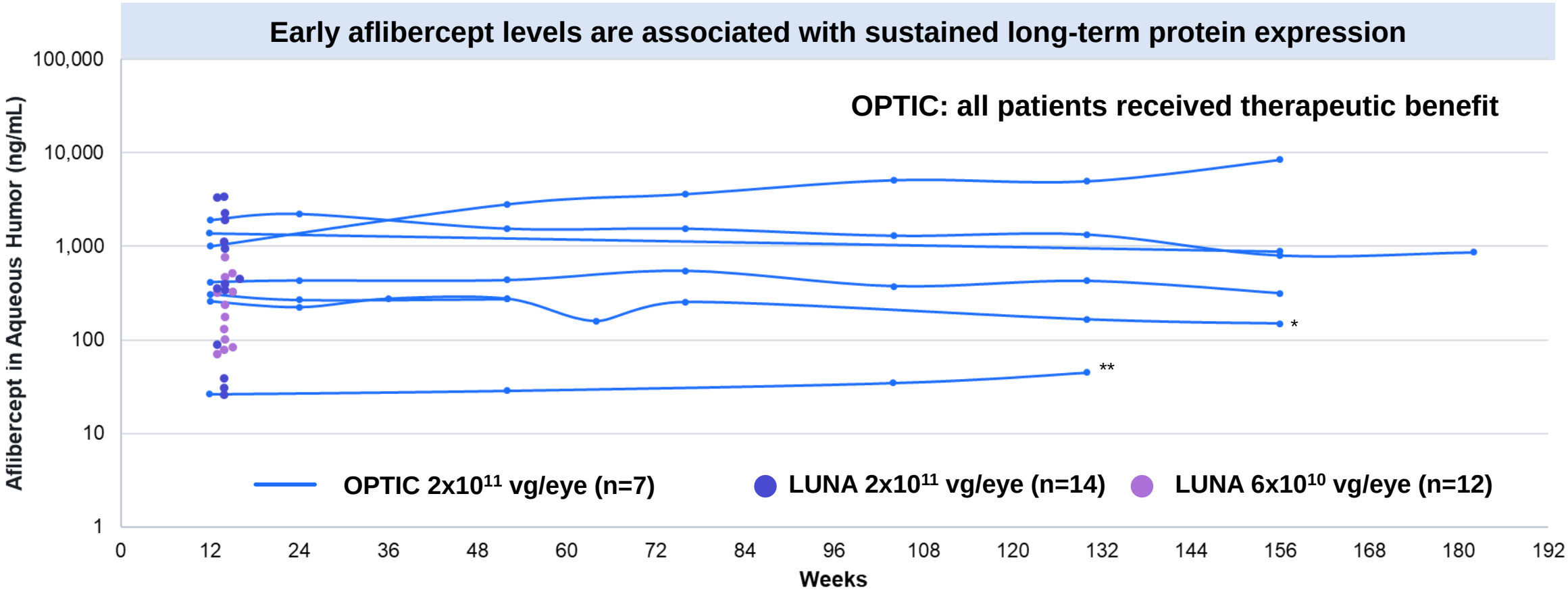
Data cut: 15Nov2023

LUNA Demographics and Baseline Characteristics

Demographics and Baseline Characteristics	Ixo-vec $6x10^{10}$ vg/eye N = 30	Ixo-vec $2x10^{11}$ vg/eye N = 30	LUNA Total N = 60
Mean age, years (SD)	75.4 (8.2)	77.7 (7.4)	76.6 (7.8)
Female, n (%)	16 (53%)	18 (60%)	34 (57%)
Race, n (%)			
White	27 (90%)	28 (93%)	55 (92%)
Asian	2 (7%)	2 (7%)	4 (7%)
Mean years since nAMD diagnosis in the study eye (SD)	2.6 (2.7)	2.8 (3.3)	2.7 (3.0)
Mean annualized anti-VEGF injections prior to Day 1 (SD)	10.0 (1.7)	9.7 (2.5)	9.9 (2.1)
Mean BCVA, ETDRS letters (SD)	72.9 (8.8)	71.8 (6.4)	72.3 (7.7)
Mean CST, μm (SD)	360.6 (112.0)	340.5 (119.3)	350.6 (115.2)
Phakic lens status, n (%)	10 (33%)	11 (37%)	21 (35%)

Data cut: 15Nov2023

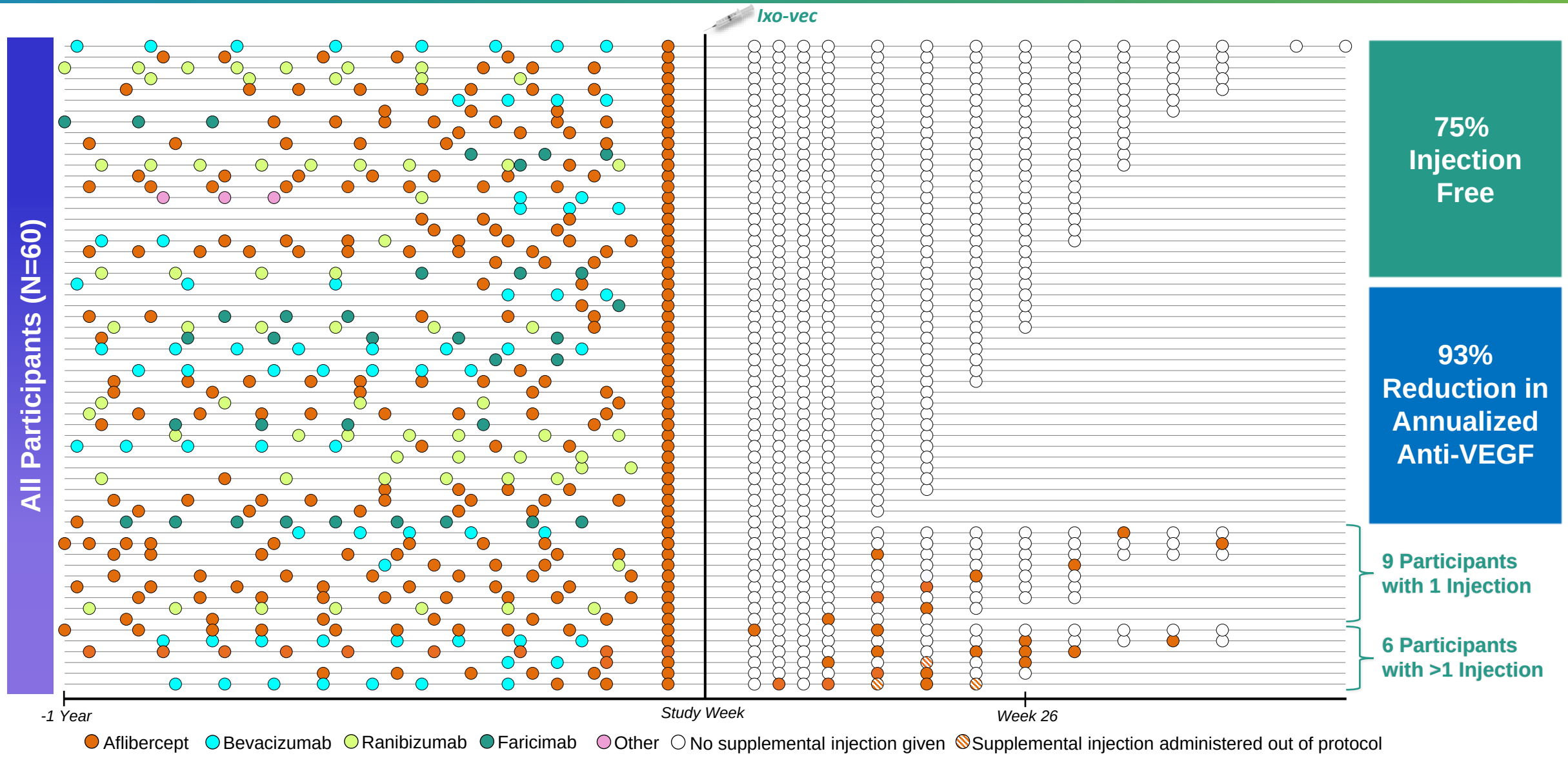
Aqueous Aflibercept Levels at Both Doses in LUNA Demonstrate Ixo-vec Therapeutic Benefit



OPTIC and LUNA: no minimum aqueous humor aflibercept threshold for clinical benefit observed

*Data cut: 15Nov2023. 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.*

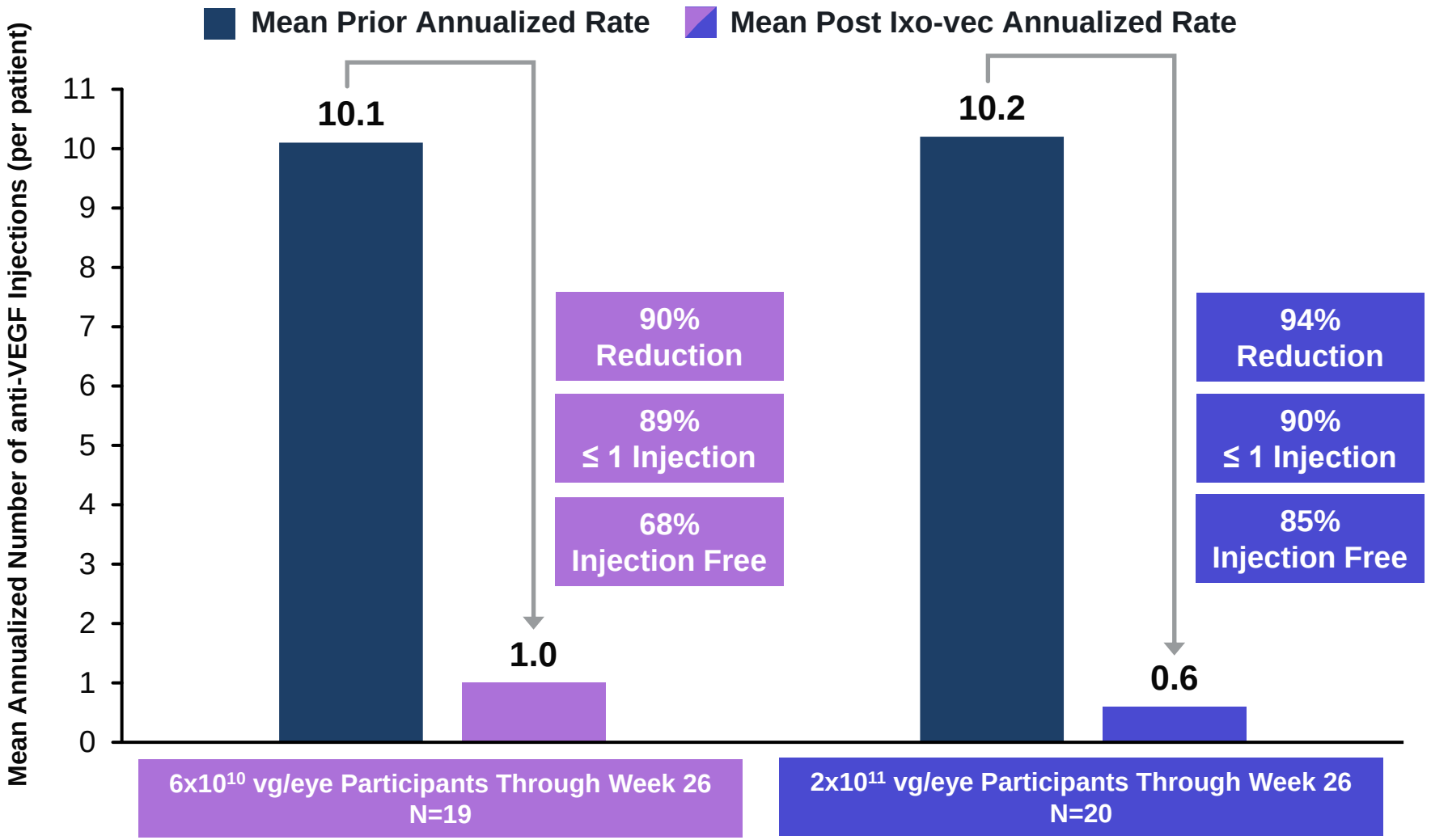
93% Anti-VEGF Treatment Burden Reduction Across Both Doses of Ixo-vec in a Heavily Pretreated nAMD Population



Doses pooled to preserve investigator masking in an ongoing double masked study. 71% reduction of annualized injections across both doses in subset of patients who received supplemental Injections.
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) = (numbers of aflibercept IVTs since Ixo-vec) / (days from Ixo-vec to the last study follow-up / 365.25). Reduction in annualized anti-VEGF is based on all participants through most recent visit

Data cut: 02Jan2024

90-94% Reduction in Mean Annualized Anti-VEGF Injections with 89-90% ≤1 and 68-85% Free of Injections Through Week 26

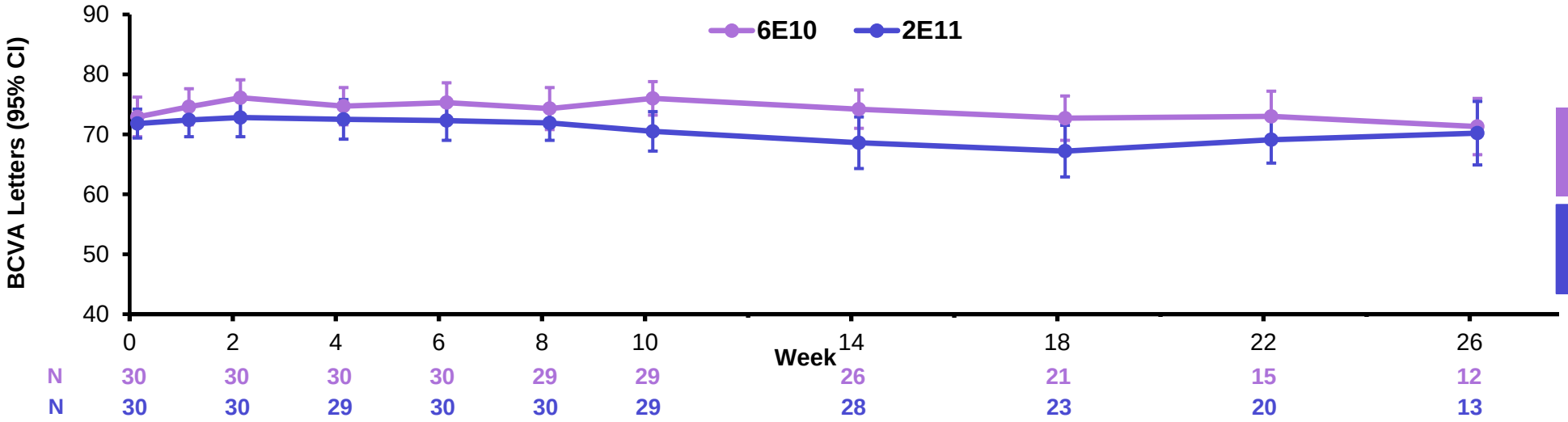


Annualized rate (Prior) = (number of IVTs in 12 months prior to Ixo-vec) / (days from the first IVT in the past 12 months to Ixo-vec / 365.25).
Annualized rate (Post) = (numbers of aflibercept IVTs since Ixo-vec) / (days from Ixo-vec to the last study follow-up / 365.25).
Reduction in annualized anti-VEGF through Week 26 among participants who have completed Week 26
VEGF, vascular endothelial growth factor; IVT: intravitreal.

Data cut: 02Jan2024

Stable Vision and Anatomic Control Maintained Through 26 Weeks in Both Ixo-vec Dose Groups

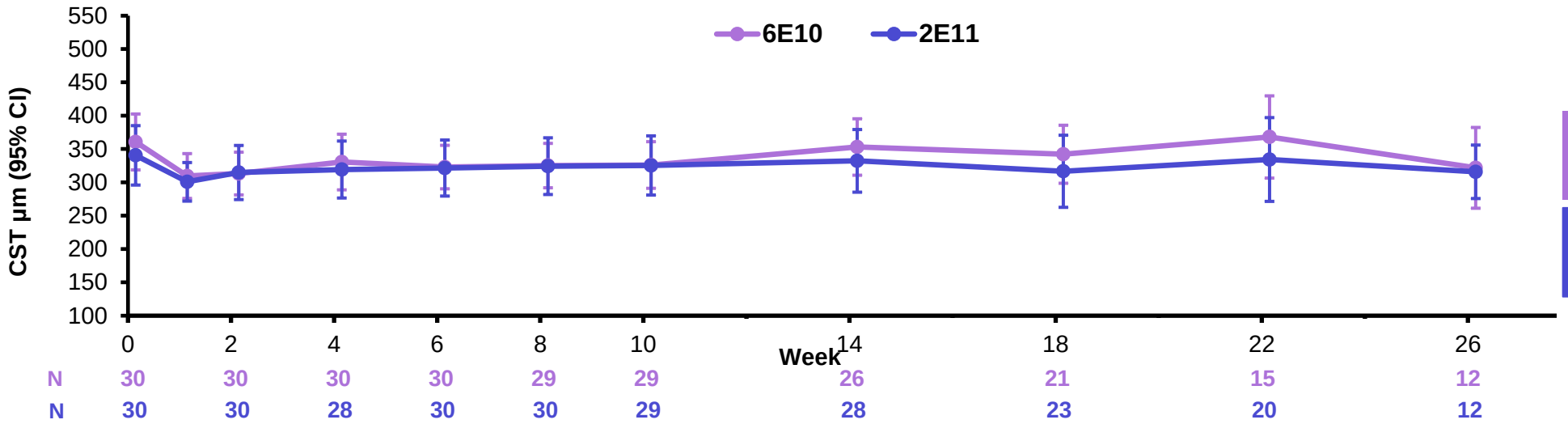
Best Corrected Visual Acuity (BCVA) Over Time by Dose



Mean BCVA change from baseline to last visit, letters (95% CI)

- 0.5 (-2.2, 3.3) 6x10^{10} vg/eye
- -1.7 (-4.5, 1.2) 2x10^{11} vg/eye

Central Subfield Thickness (CST) Over Time by Dose



Mean CST change from baseline to last visit, µm (95% CI)

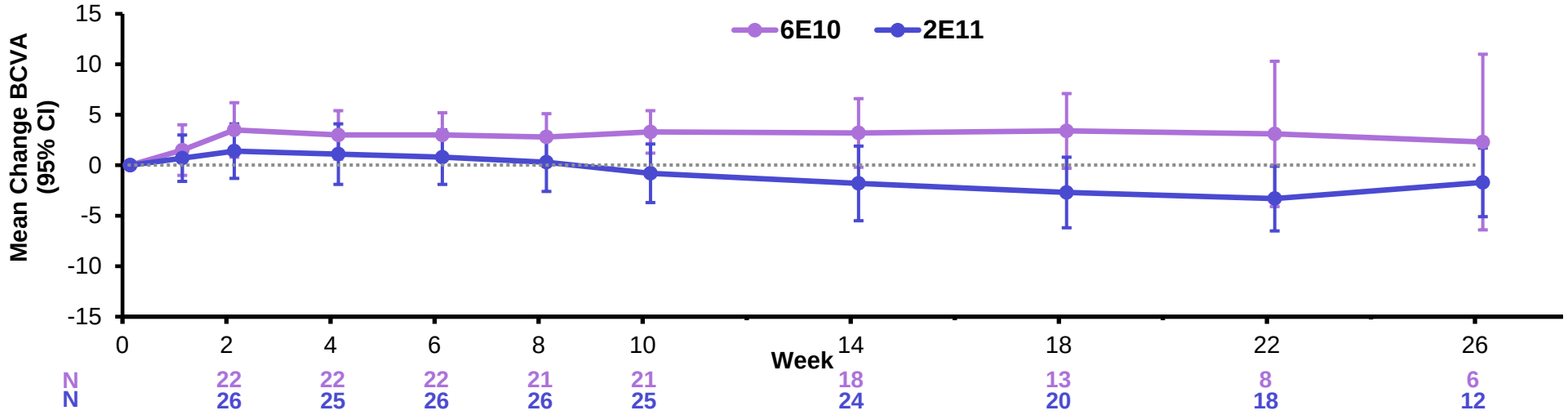
- -7.9 (-30.9, 15.0) 6x10^{10} vg/eye
- -16.4 (-31.5, -1.3) 2x10^{11} vg/eye

CST measurement missing for one participant at week 4 and week 26

Data cut: 15Nov2023

Stable Visual and Anatomic Control Maintained in Supplemental Injection Free Patients

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

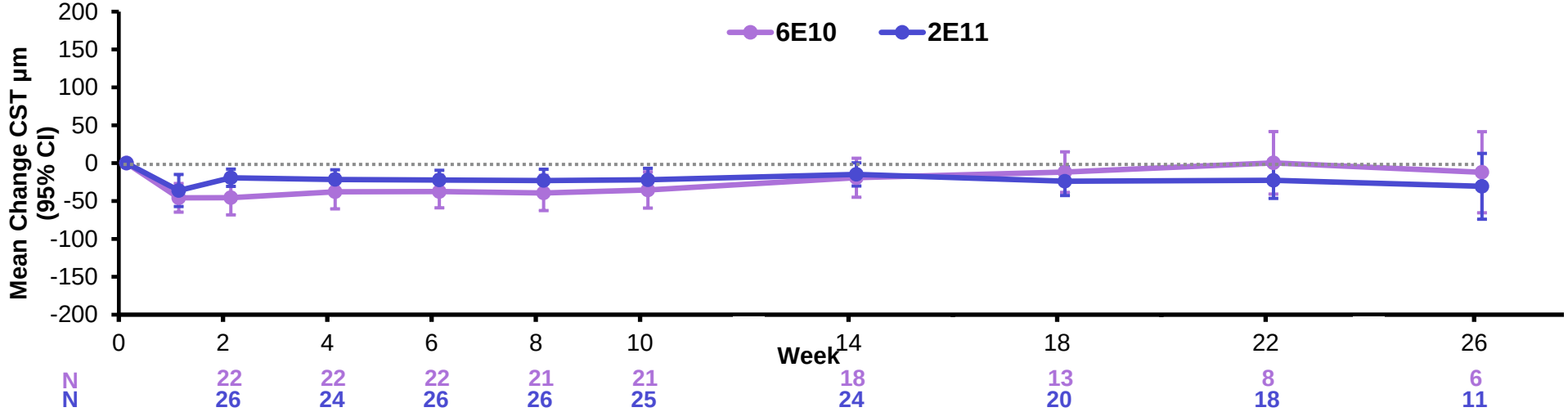


Mean BCVA change from baseline to last visit, letters (95% CI)

+2.7 (0.0, 5.4)
6x10^{10} vg/eye

-1.2 (-4.1, 1.7)
2x10^{11} vg/eye

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



Mean CST change from baseline to last visit, µm (95% CI)

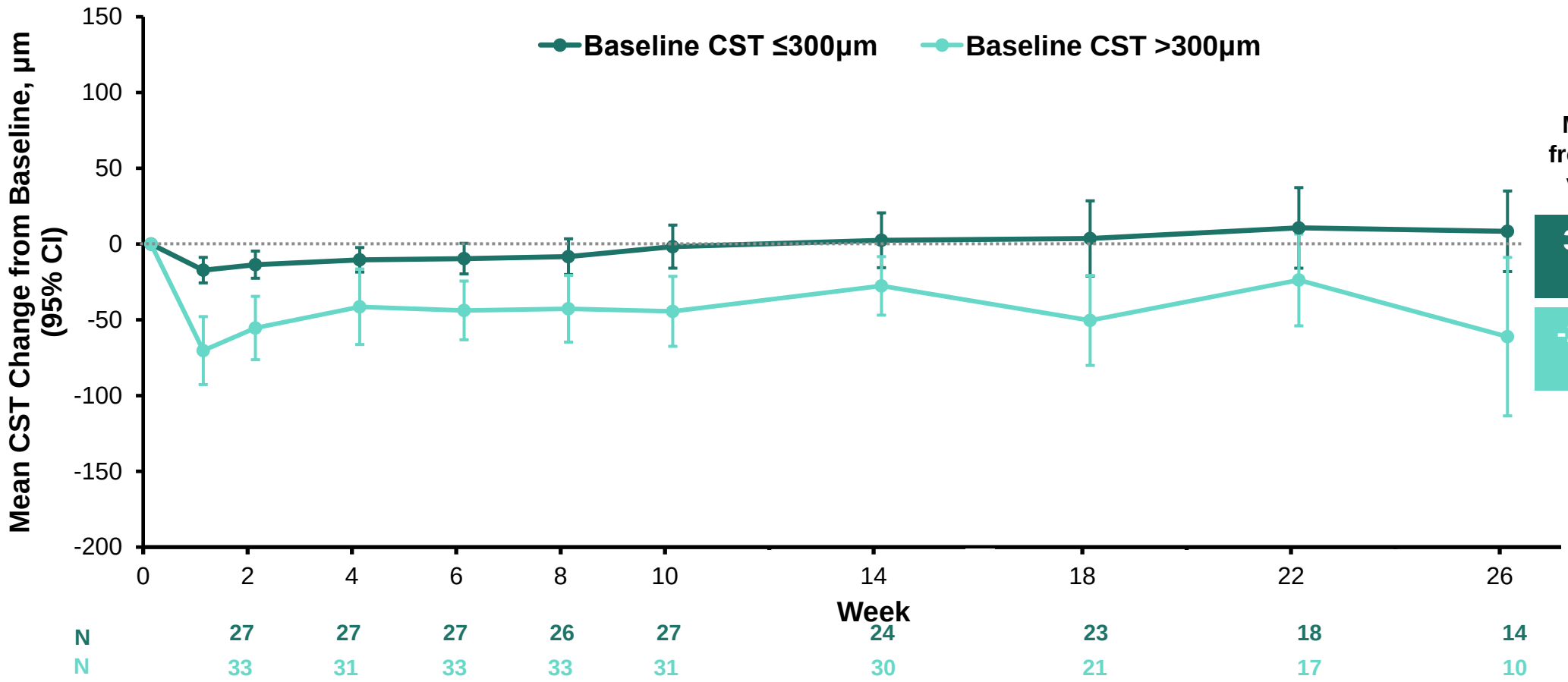
-2.8 (-19.7, 14.2)
6x10^{10} vg/eye

-14.8 (-32.1, 2.4)
2x10^{11} vg/eye

CST measurement missing for one participant at week 4 and week 26

Data cut: 15Nov2023

Anatomic Control Maintained with Greater CST Reduction Among Participants with Baseline CST >300 µm



Mean CST change from baseline to last visit, µm (95% CI)

3.4 (-11.1, 17.9)
BL ≤300 µm

-24.9 (-45.8, -4.0)
BL >300 µm

Baseline Characteristic for Subgroup	CST ≤300 µm	CST >300 µm
Mean CST, µm (SD)	270 (19)	417 (119)

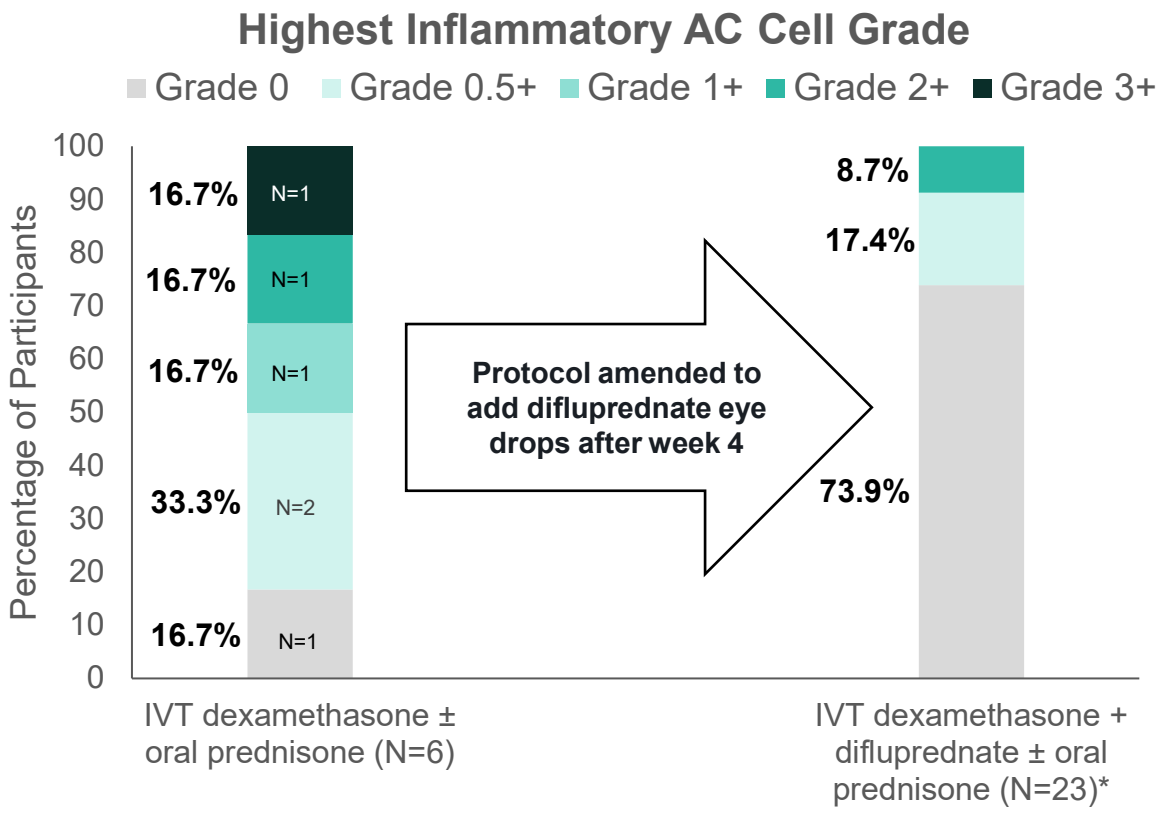
Baseline

CST measurement missing for one participant at week 4 and week 26

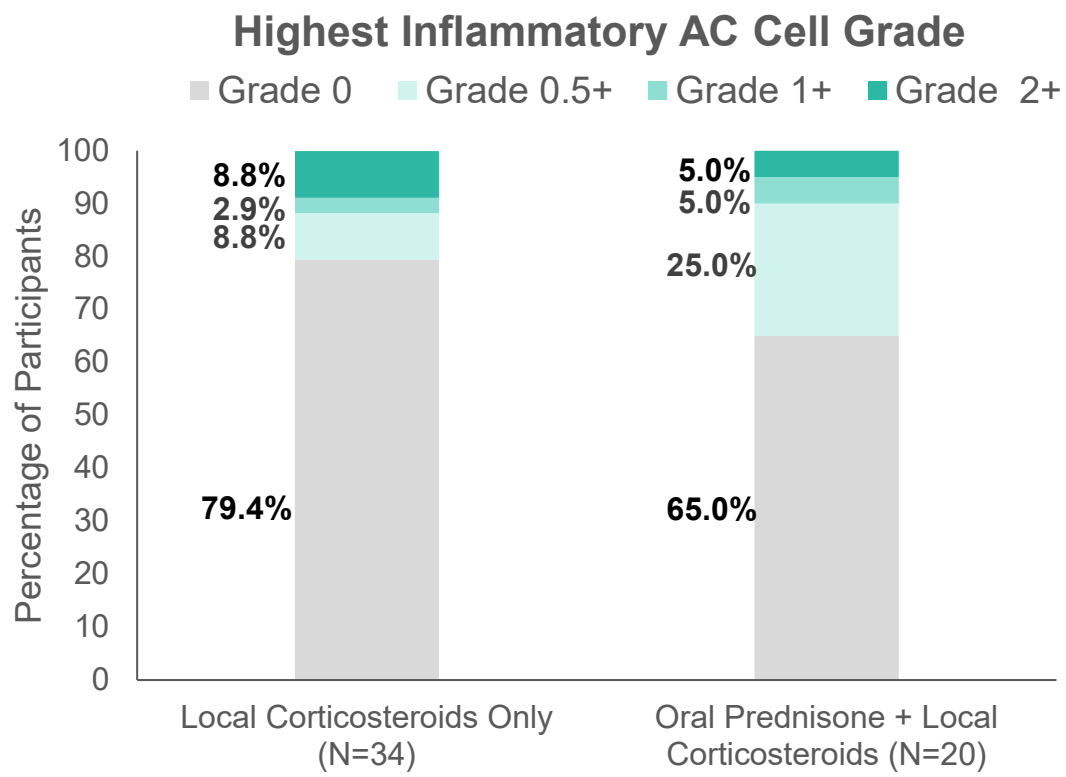
Data cut: 15Nov2023

Preliminary Safety Analysis
Prophylaxis for Ixo-vec IVT Gene Therapy Key Learnings

Observed Benefit of Difluprednate Added to IVT Dexamethasone



No Observed Benefit of Oral Prednisone

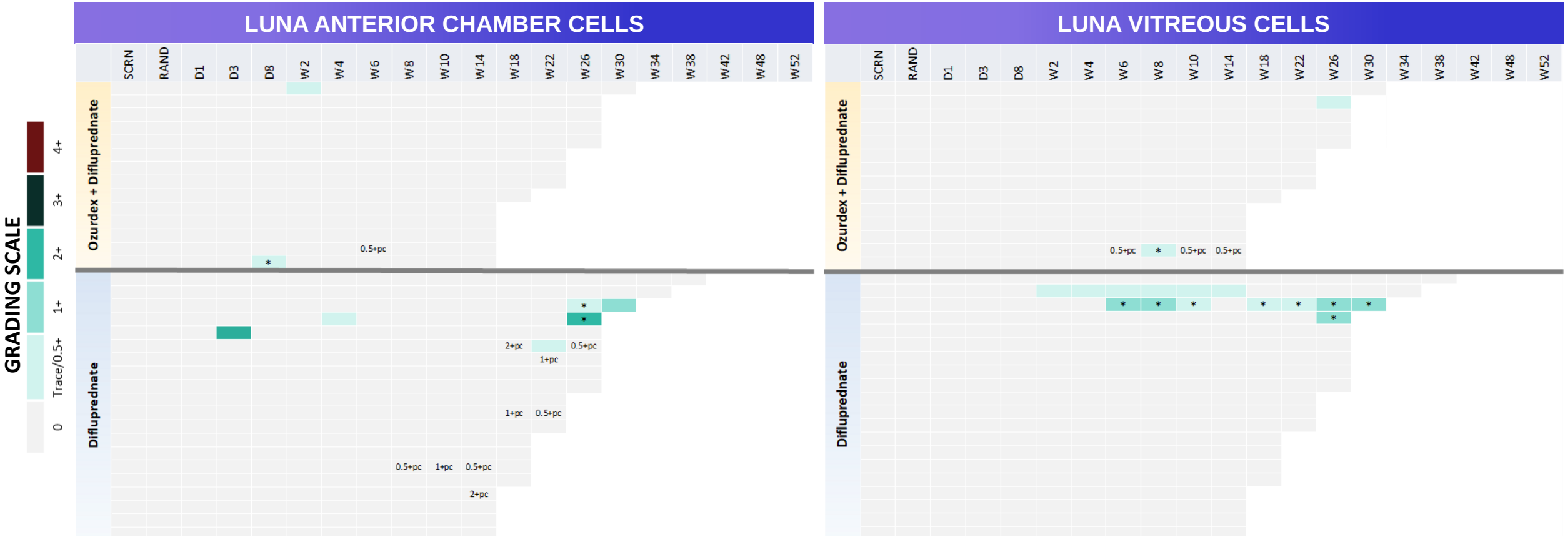


*AC: anterior chamber cell. 100% pigmented cells excluded from analysis. One participant in IVT dexamethasone alone arm had a single visit with 3+ AC cells that responded to local corticosteroids. *Includes one participant who received IVT dexamethasone + difluprednate with 2+ AC cells at a single timepoint during an unscheduled visit. Protocol amended early in study to include difluprednate after week 4 to match the taper in difluprednate regimens. 4+ AC cells due to Staph. epidermidis+ endophthalmitis post-AC tap (unrelated to Ixo-vec) in one participant excluded. Cell grades as assessed by slit lamp, Grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria for white blood cells*

Data cut: 15Nov2023

Potential Go Forward Prophylaxis Options: IVT Dexamethasone + Difluprednate or Difluprednate Alone

Preliminary LUNA data indicate that ocular inflammation is primarily located in anterior chamber, mild to moderate, and responsive to local corticosteroids[1]

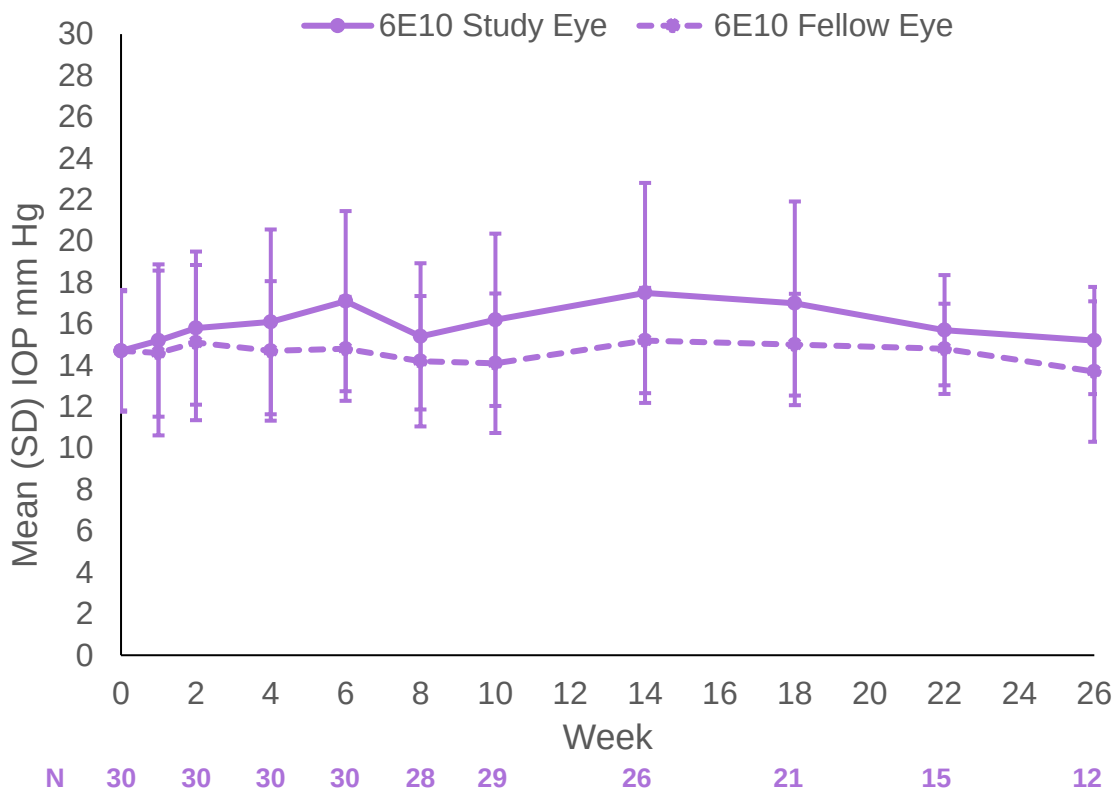


*Data cut: 15Nov2023. No participant in the displayed arms had more than 2+. *Mixed pigmented and non-pigmented cells; pc, pigmented cell. 1. Includes post-data cut review of outcomes in 4 individual patients. The second patient in the LUNA Vitreous Cells Heatmap had 0.5+ vitreous cells in both eyes starting from Week 4 with both eyes resolving at Week 18. 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.*

Mean Intraocular Pressure Stable at Both Ixo-vec Doses

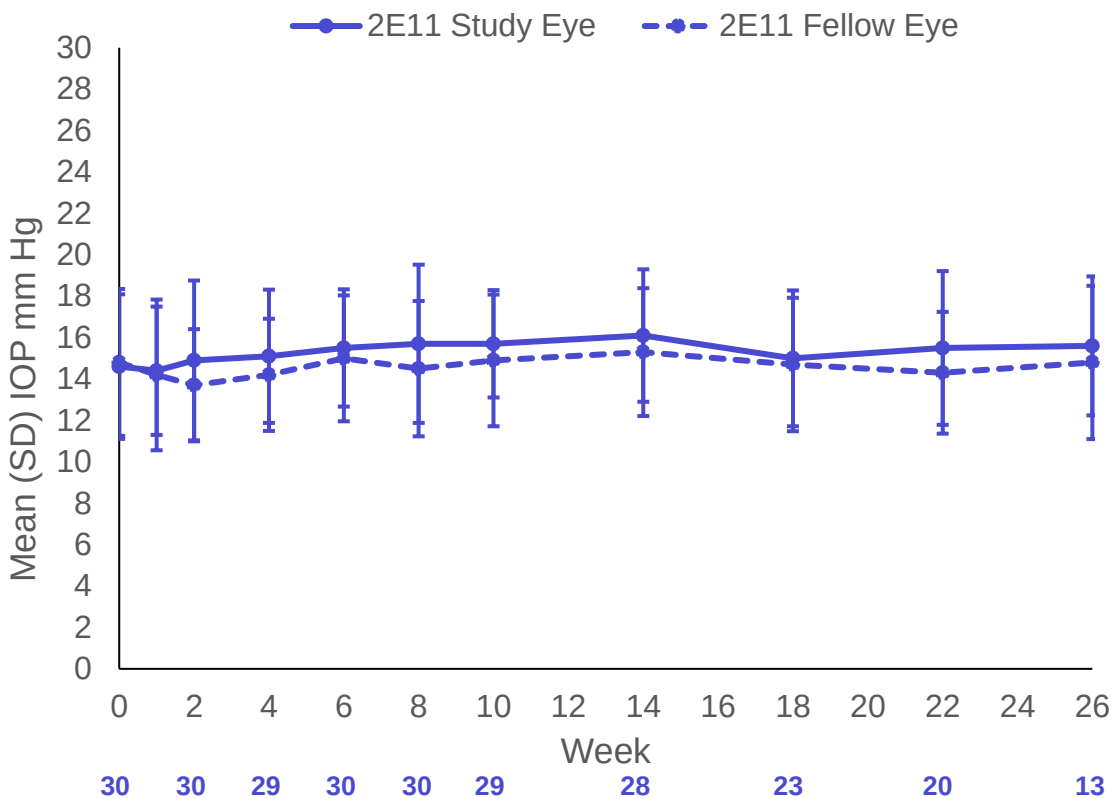
Mean IOP Over Time by Dose

6x10^{10} vg/eye



N	30	30	30	30	28	29	26	21	15	12

2x10^{11} vg/eye



30	30	29	30	30	29	28	23	20	13

Data cut: 15Nov2023

LUNA Preliminary Safety Summary

- Ixo-vec was well tolerated at both doses of $6x10^{10}$ and $2x10^{11}$ vg/eye
  - No Ixo-vec-related serious adverse events
    - One ocular SAE not related to Ixo-vec (Staph. epidermidis+ endophthalmitis post-AC tap) - resolved
  - All Ixo-vec-related AEs were either mild or moderate
    - Most common Ixo-vec-related AEs were dose-dependent anterior inflammation and anterior pigmentary changes, consistent with OPTIC study results[1]
    - Inflammation was responsive to protocol-defined local corticosteroids
  - No episcleritis, vasculitis, retinitis, choroiditis, vascular occlusion or hypotony
- Optimized prophylaxis in LUNA resulted in an improved inflammatory profile compared to $2x10^{11}$ vg/eye in the OPTIC study[2]
  - Oral corticosteroids showed no incremental benefit
  - IVT dexamethasone alone (± oral prednisone) did not provide adequate prophylaxis
  - IVT dexamethasone + difluprednate regimen resulted in > 90% of participants having no or minimal inflammation (0 or trace/0.5+ AC cells) during the period of peak inflammatory response

1. *Khanani AM et al. Lancet eClinical Medicine. 2024*
2. *Khanani AM. Retina Society Annual Meeting Presentation 2021, Chicago, IL*

Data cut: 15Nov2023

Key Preliminary Takeaways

Efficacy

- BCVA was maintained and CST was reduced and remained stable at both Ixo-vec doses of $6x10^{10}$ and $2x10^{11}$ vg/eye, with greater CST reduction among participants with CST>300 at baseline
- Substantial treatment burden reduction observed in patients previously requiring >9 annualized anti-VEGF injections:
  - ≥ 90% reduction in annualized anti-VEGF injections in both dose groups
  - 85% and 68% of patients remain free of injections at 6 months at $2x10^{11}$ and $6x10^{10}$ doses, respectively

Safety

- Ixo-vec was well tolerated at both doses, with no Ixo-vec-related SAEs
- Two promising local prophylactic options emerging: IVT dexamethasone + difluprednate eye drops and eye drops alone
  - IVT dexamethasone + difluprednate eye drops led to > 90% of participants having no or minimal inflammation (0 or trace/0.5+ AC cells) during the period of peak inflammatory response

Next Steps

- A prespecified interim analysis will be conducted when all participants complete their 26-week study visit

Data cut: 15Nov2023

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