Ixoberogene Soroparvovec (Ixo-vec) IVT Gene Therapy for Neovascular AMD: 26-Week Interim Analysis Results from the Phase 2 LUNA Study

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57th Retina Society Congress • September 11-15, 2024

Disclosures

- This presentation discussed IRB/IEC approved research of an investigational medicine
- Studies funded by Adverum
- Mark Barakat has the following financial interests or relationships to disclose:

AbbVie Inc[C]
Adverum Biotech[CR]
Alcon[BC]
Alimera[C]
Allegro[C]
Allergan[C]
AmerisourceBergen[C]
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Oxular[R]
Oxurion[ER]
Perfuse[R]
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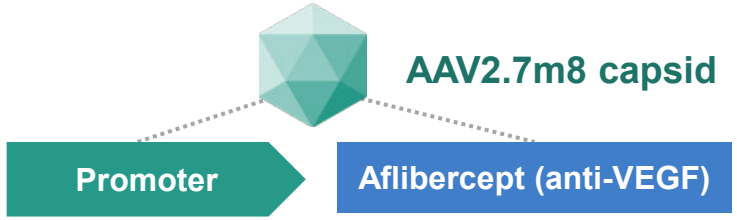
ReNeuron[R]
RevOpsis Therapeutics[CE]
Ribomic[R]
Roche[C]
Stealth Biotherapeutics[CR]
Unity Biotechnology[R]

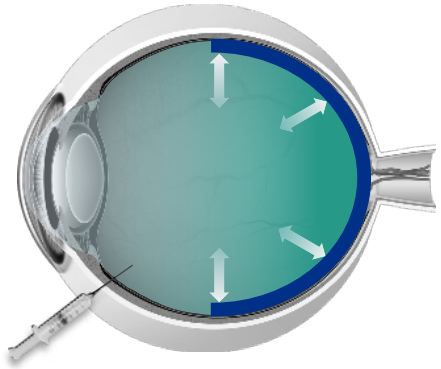
(B): Speakers' Bureau; (C): Consultant; (E): Equity; (R): Grants/Research Support

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



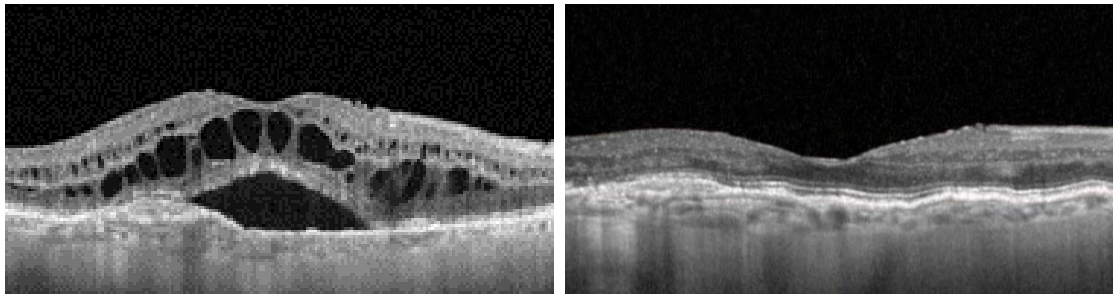
Following a one-time IVT Ixo-vec injection, transduced retinal cells become the source of continual aflibercept production



IVT injection of Ixo-vec

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

nAMD OPTIC $2x10^{11}$ vg/eye 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

LUNA Phase 2 Trial in Previously Treated Patients with nAMD

To Evaluate Lower Doses of Ixo-vec and Enhanced Corticosteroid Prophylaxis Regimens

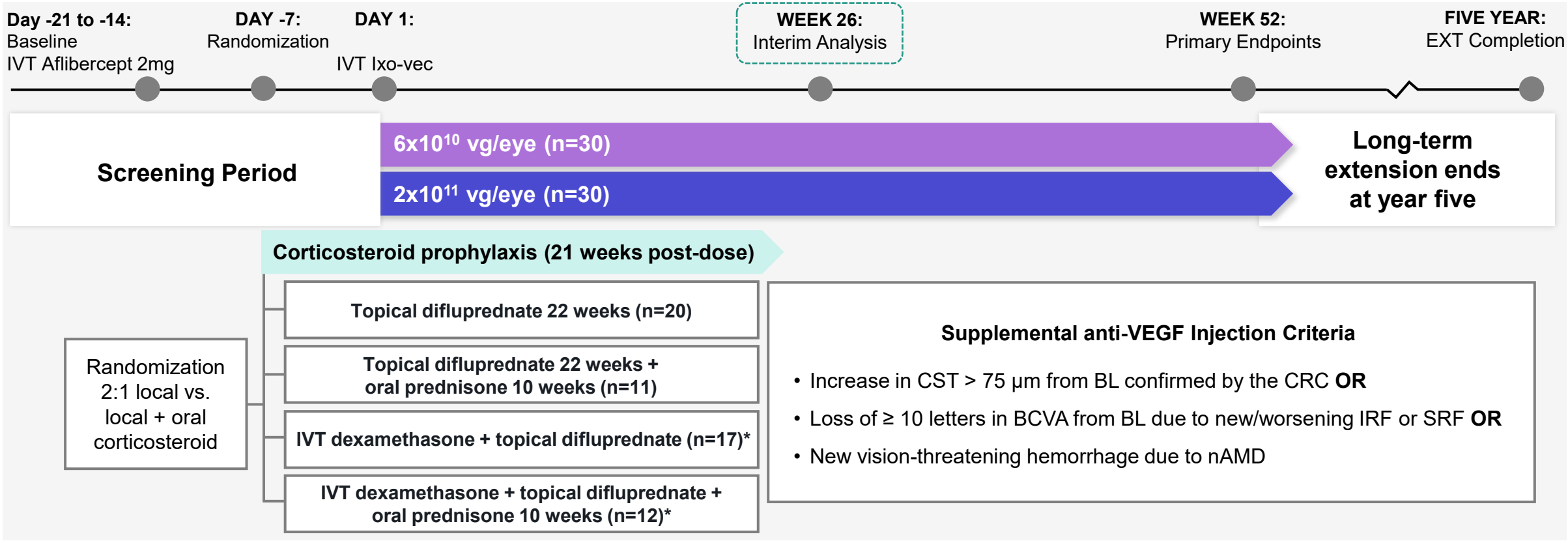
Multicenter, double-masked, randomized, parallel-group Phase 2 study

Key inclusion criteria

- Demonstrated response to anti-VEGF therapy and under active treatment for choroidal neovascularization 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 through Week 52
- Incidence and severity of adverse events through Week 52



*Study timeline and length of arrows depicted are not to scale. Baseline is defined as the day screening aflibercept is administered. Investigators and participants are masked to the dose of Ixo-vec; they are not masked to the corticosteroid prophylaxis regimen. *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 topical 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*

LUNA Study Disposition

Participant Disposition	
Number of participants randomized and dosed with Ixo-vec	60
Number of participants who completed Week 26	58
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	35.2

Prespecified interim analysis performed when all participants completed the 26-week study visit

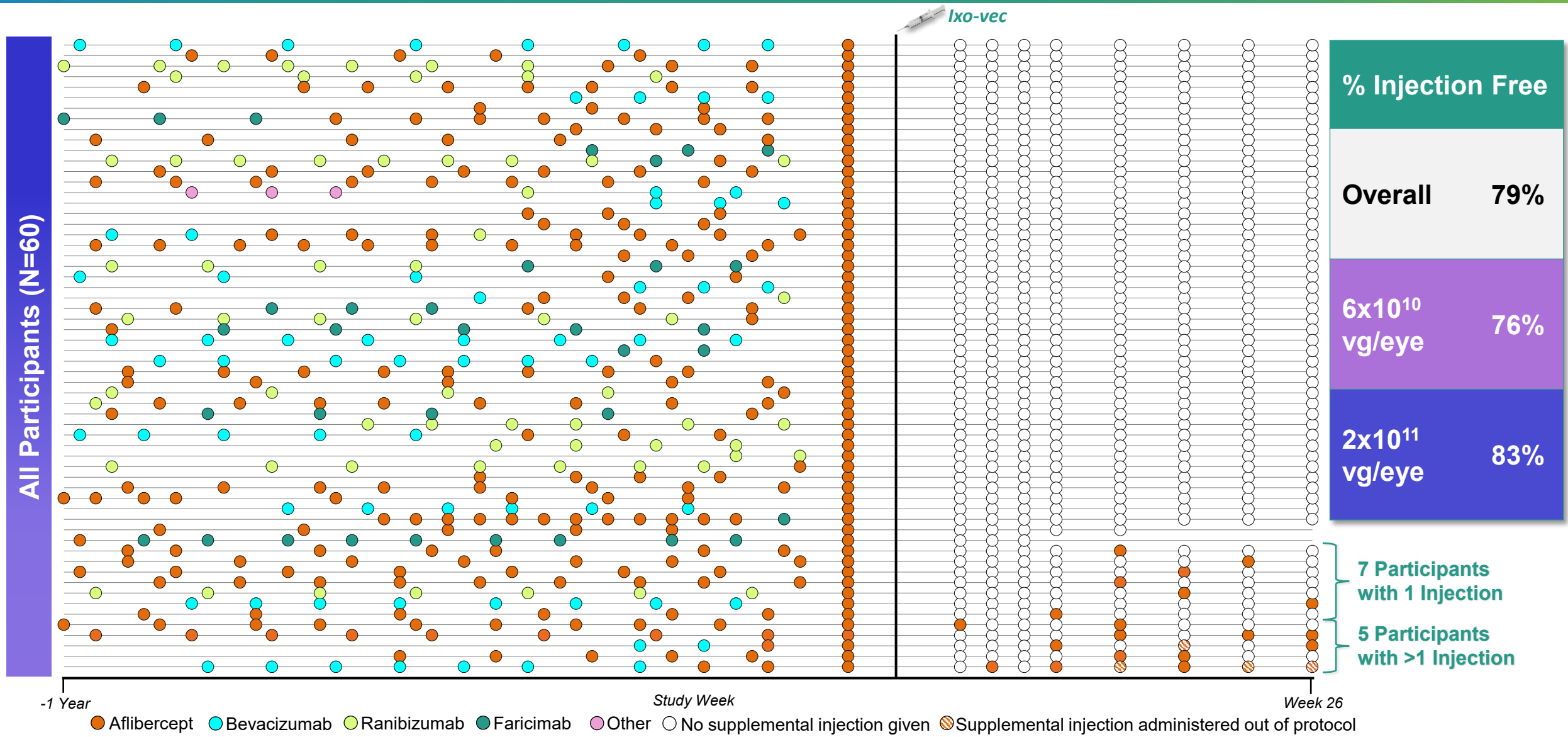
Data cut: 14Feb2024

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)	3.0 (2.9)	3.0 (3.1)	3.0 (2.9)
Mean annualized anti-VEGF injections in year prior to Day 1 (SD)	10.2 (1.7)	10.0 (3.3)	10.1 (2.6)
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 (%)	11 (37%)	11 (37%)	22 (37%)

Data cut: 14Feb2024

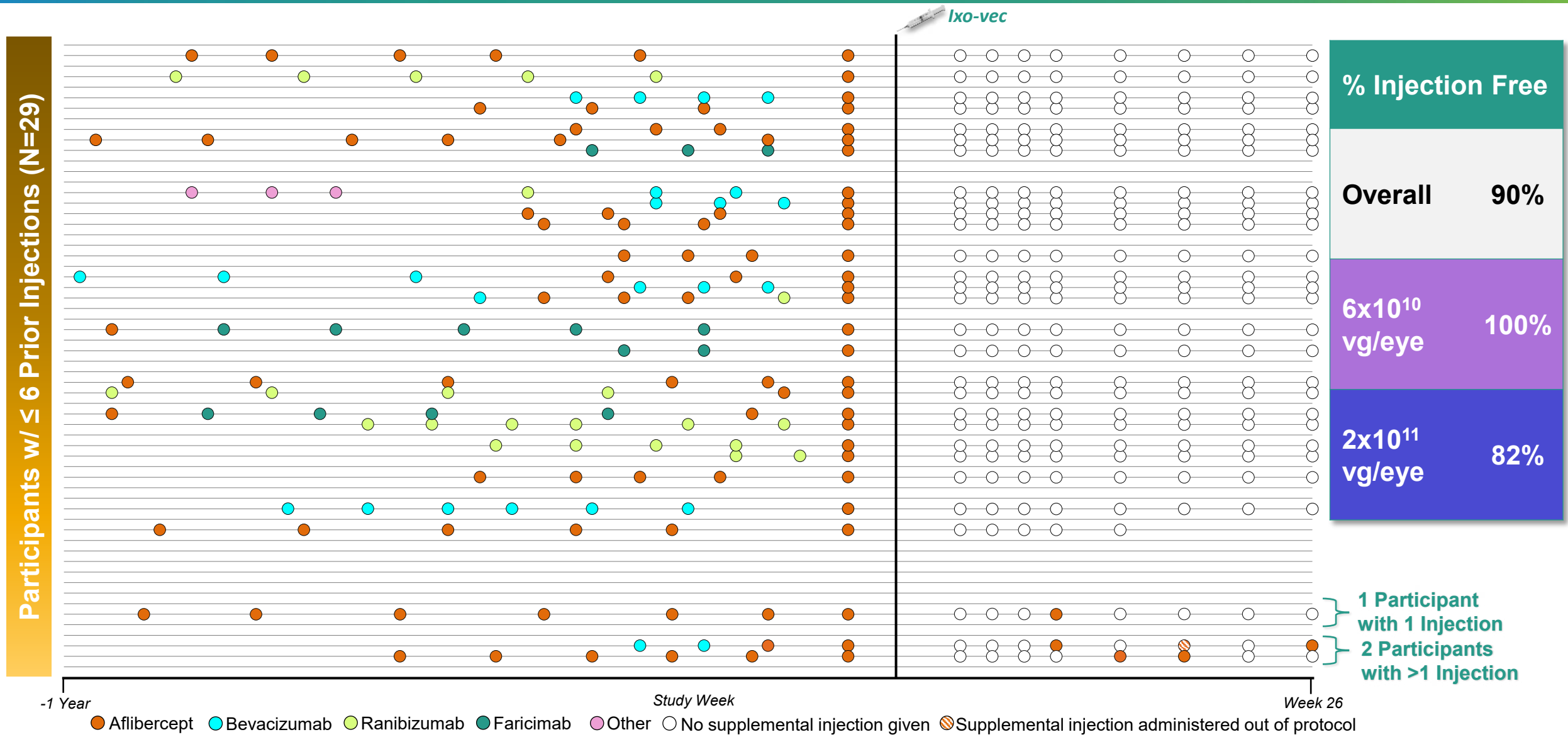
79% were Injection Free Across Both Ixo-vec Doses in Patients Previously Requiring Frequent Anti-VEGF Injections



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

Data cut: 14Feb2024

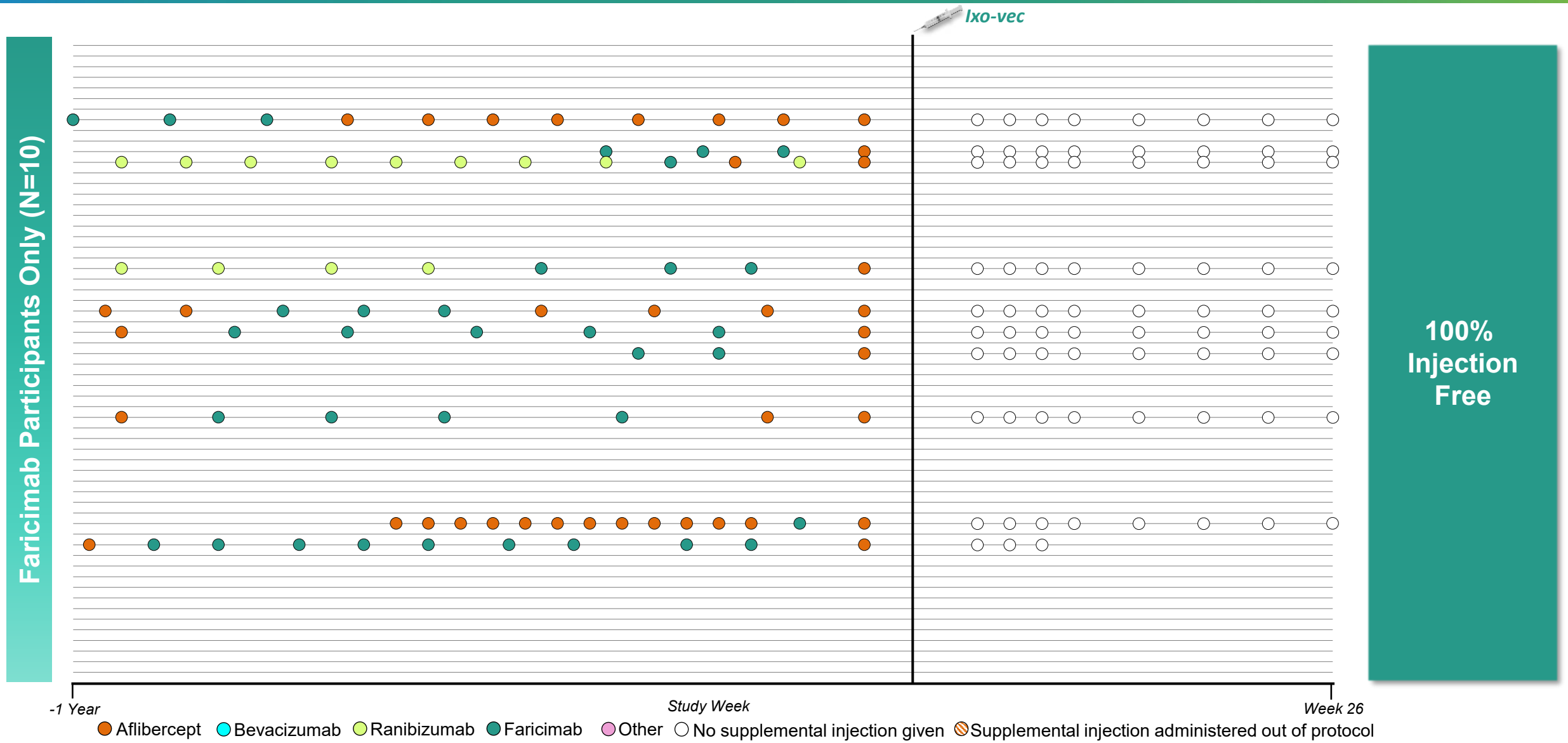
90% were Injection Free Across Both Ixo-vec Doses in Patients with ≤ 6 Prior Injections in the Year Prior



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.

Data cut: 14Feb2024

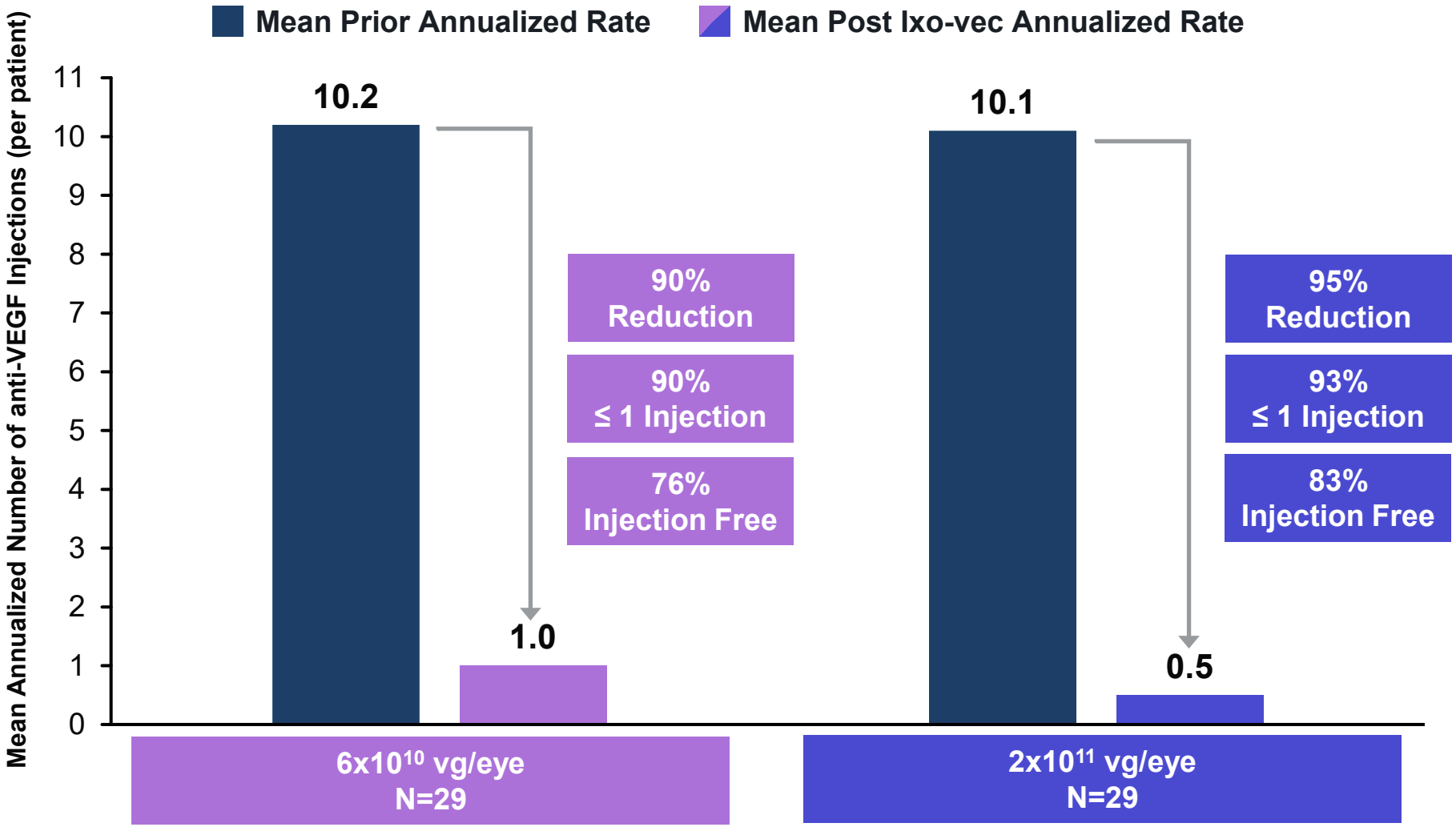
100% of Patients Previously Receiving Faricimab Remain Injection Free



Doses pooled in swim lane plot to preserve investigator masking in an ongoing double masked study. Patients who received faricimab in the year prior to receiving Ixo-vec. These received approximately 10 annualized injections in the year prior to Ixo-vec.

Data cut: 14Feb2024

90-95% Anti-VEGF Treatment Burden Reduction Across Both Ixo-vec Doses

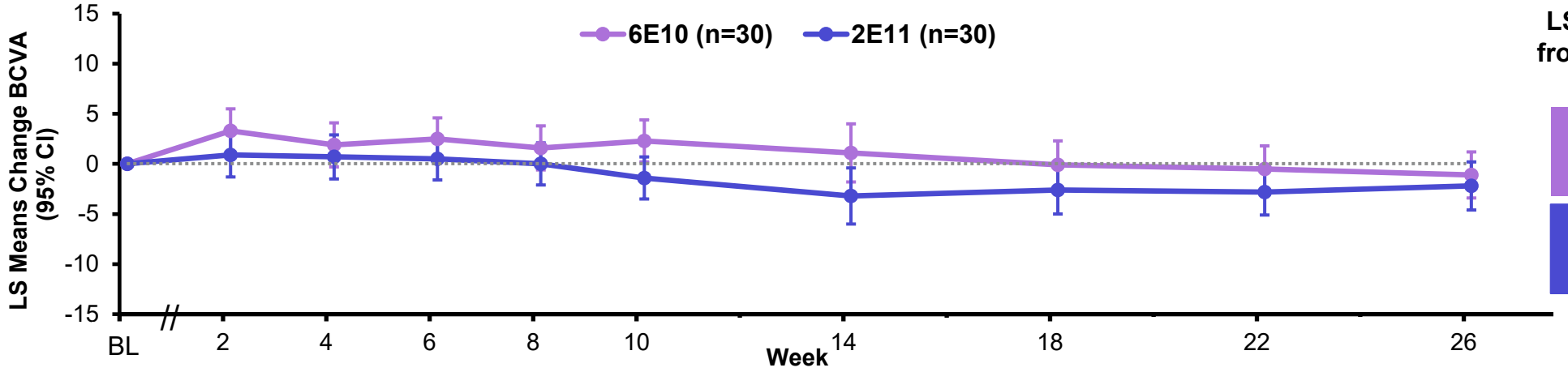


Annualized rate (Prior) = (number of IVTs in 12 months prior to Ixo-vec) / (days from the first IVT in the past 12 months to Ixo-vec / 365.25).
Annualized rate (Post) = (numbers of aflibercept IVTs since Ixo-vec) / (days from Ixo-vec to last follow-up within the interim analysis period / 365.25).
VEGF, vascular endothelial growth factor; IVT: intravitreal.

Data cut: 14Feb2024

Both Doses of Ixo-vec Maintained Visual & Anatomic Outcomes

Least Squares Means Change in Best Corrected Visual Acuity (BCVA) Over Time by Dose



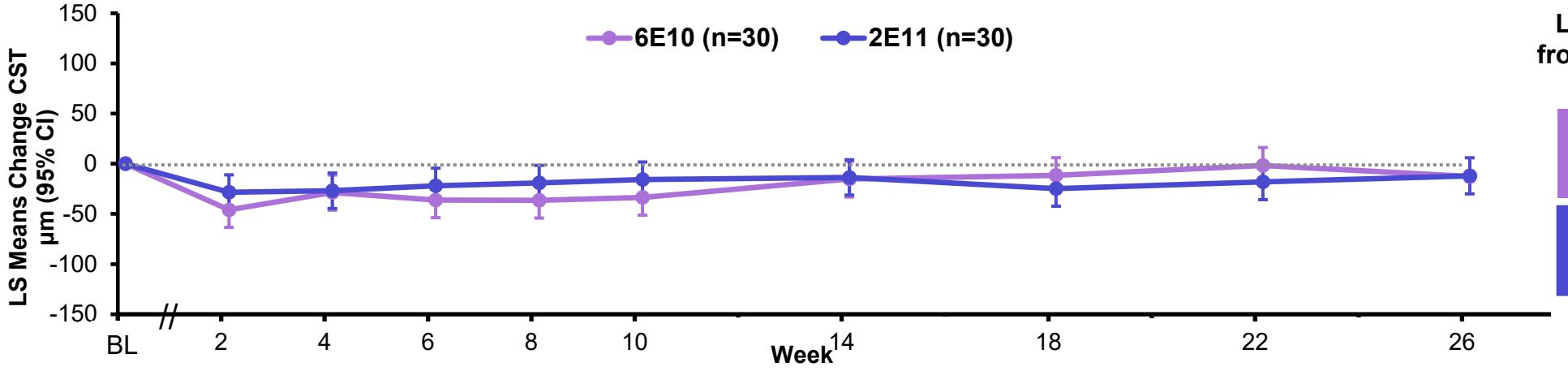
LS Means BCVA Change from Baseline at Week 26, Letters (95% CI)

-1.1 (-3.5, 1.2)
6x10^{10} vg/eye

-2.2 (-4.5, 0.2)
2x10^{11} vg/eye

p = 0.52

Least Squares Means Change in Central Subfield Thickness (CST) Over Time by Dose



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

-12.6 (-30.2, 5.0)
6x10^{10} vg/eye

-12.0 (-30.0, 6.0)
2x10^{11} vg/eye

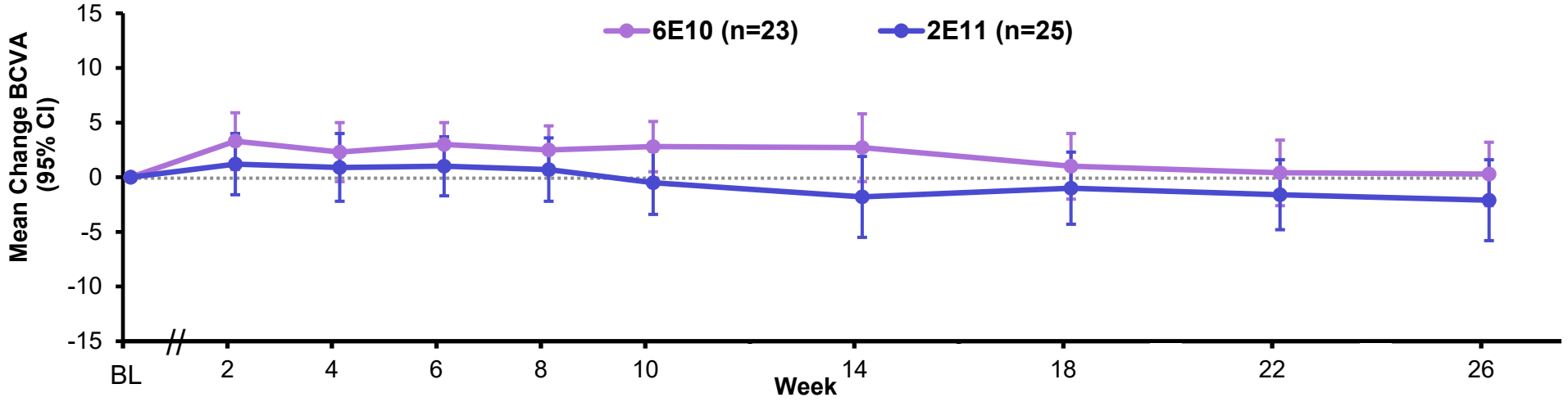
p = 0.97

*Least Squares Means are based on Mixed Model Repeated Measures (MMRM) including dose group, baseline value, visit and visit*dose group*

Data cut: 14Feb2024

Both Doses of Ixo-vec Maintained Visual and Anatomic Outcomes in Supplemental Injection-Free Participants

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

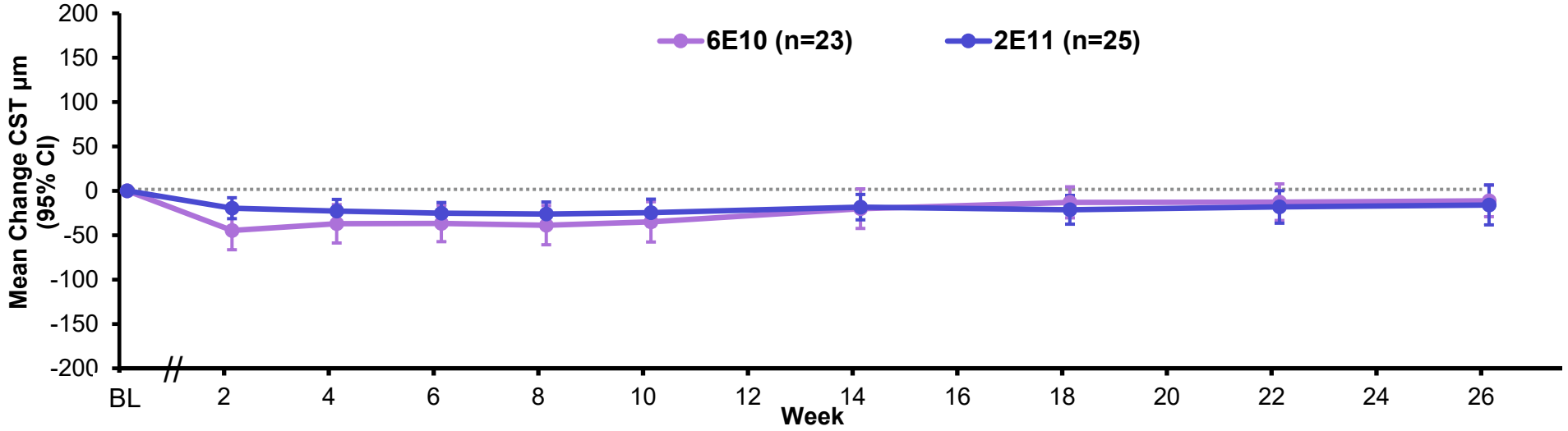


Mean BCVA Change from Baseline at Week 26, Letters (95% CI)

+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



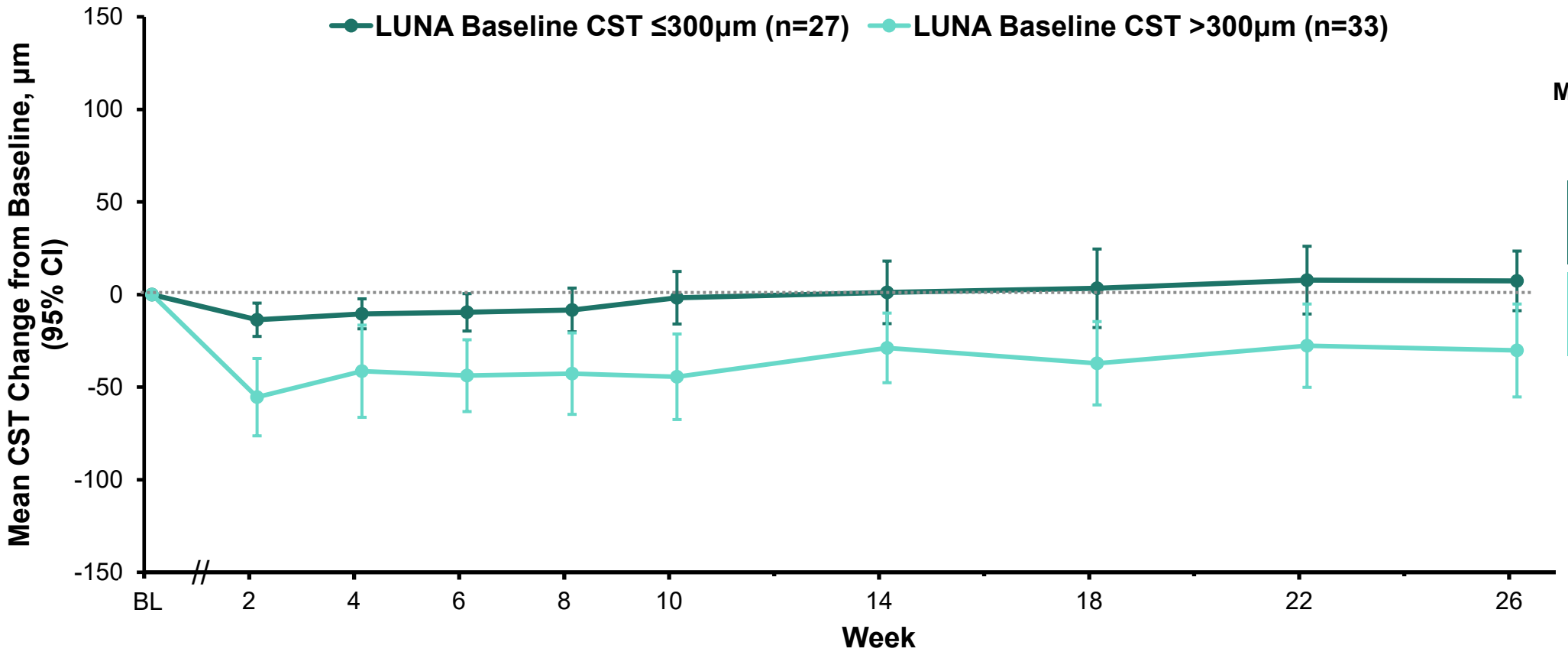
Mean CST Change from Baseline at Week 26, µm (95% CI)

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

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

Data cut: 14Feb2024

Ixo-vec Maintains Anatomic Control with Greater CST Reduction Among Participants with Baseline CST >300 µm



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

7.4 (-8.6, 23.5)
BL ≤300 µm

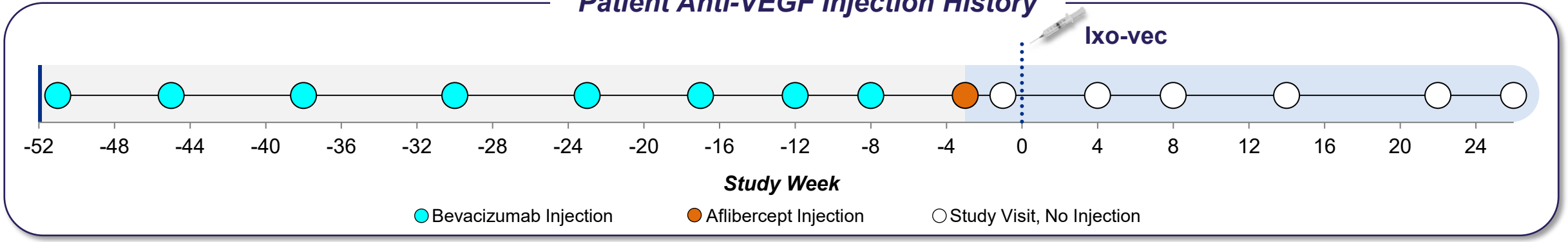
-30.2 (-55.2, -5.1)
BL >300 µm

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

Data cut: 14Feb2024

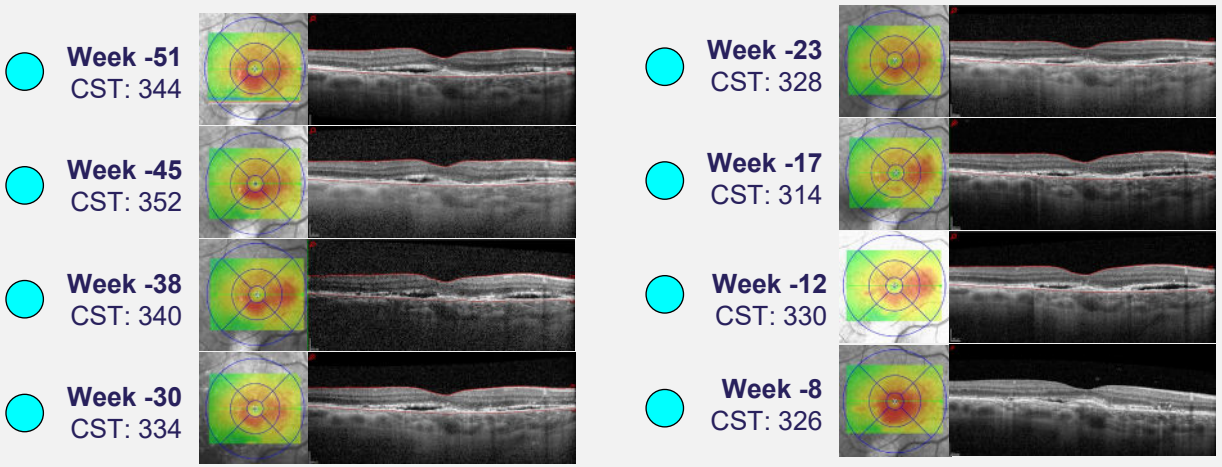
6x10[10] vg/eye Patient Case Study: Anti-VEGF Injection History

Patient Anti-VEGF Injection History



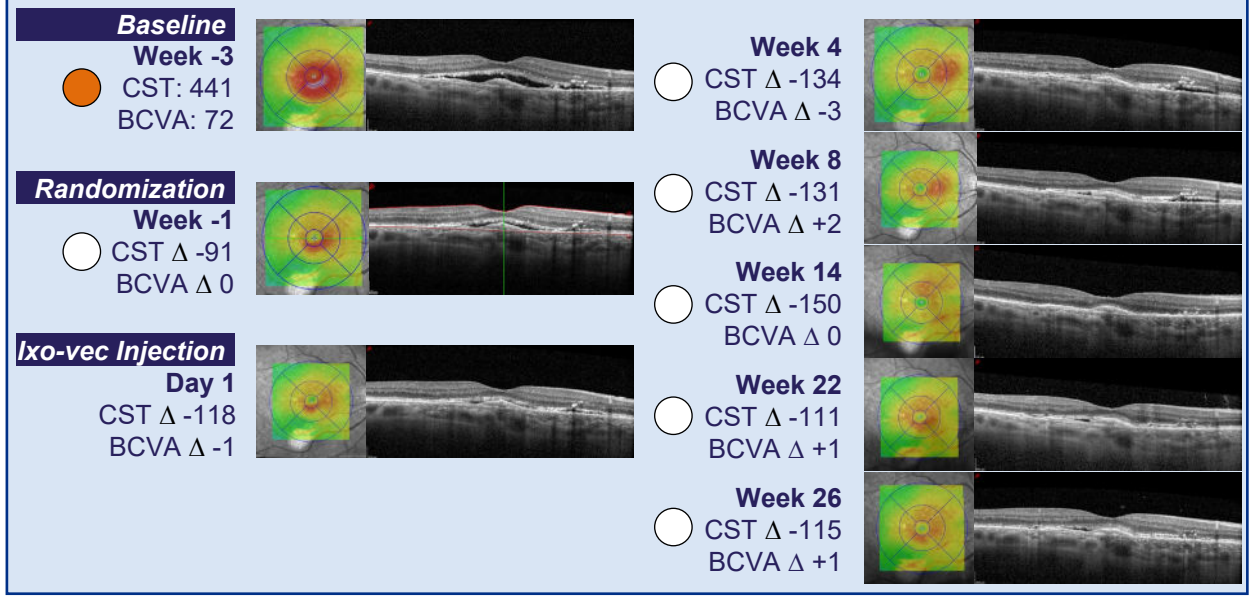
Prior To LUNA

Patient Received Bevacizumab Anti-VEGF Injections Every 4-8 Weeks



LUNA

BCVA & CST Levels Maintained With No Additional Anti-VEGF Injections Through 26 Weeks



CST, central subfield thickness, µm. BCVA, best corrected visual acuity, letters. Δ in CST and BCVA values from Baseline.

Data cut: 14Feb2024

Safety Summary of the LUNA 26-week Interim Analysis

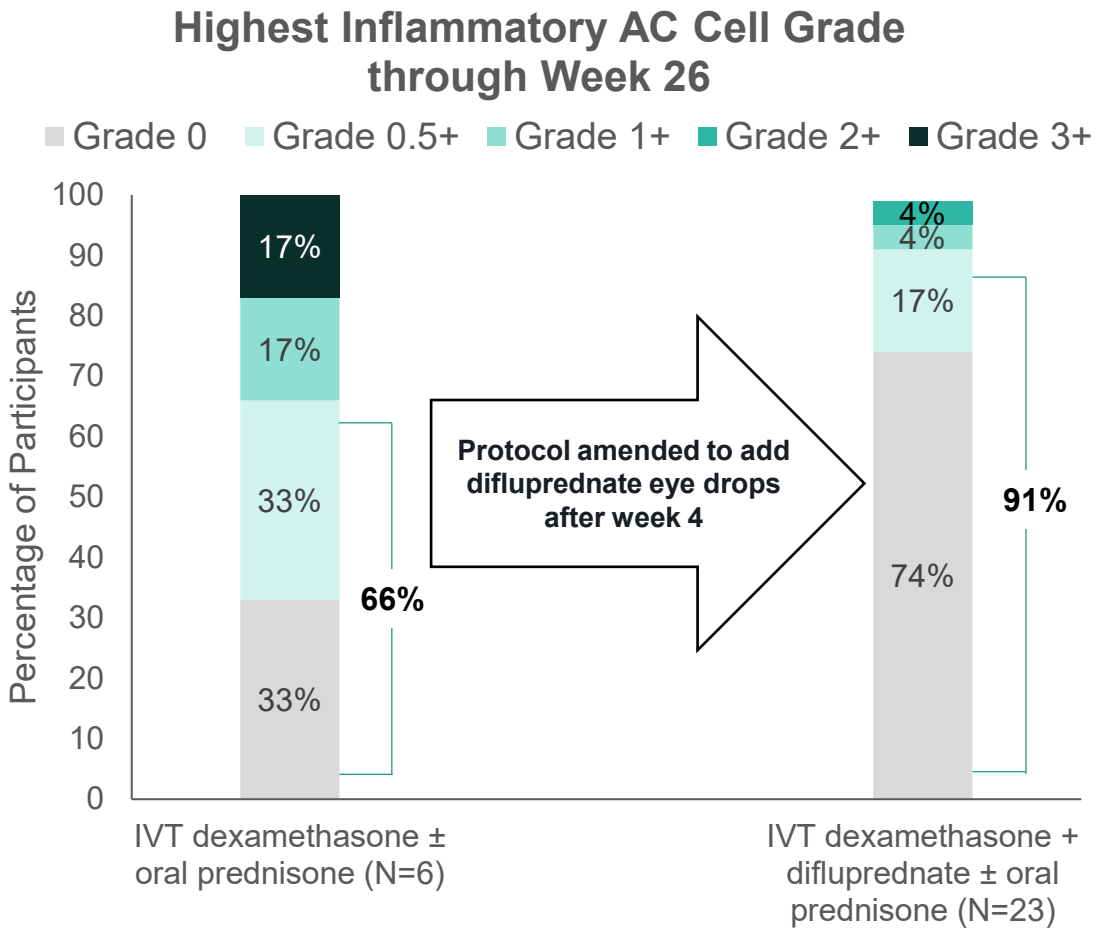
- Ixo-vec was well tolerated at both doses of $6x10^{10}$ and $2x10^{11}$ vg/eye
  - No Ixo-vec-related serious adverse events
  - No episcleritis, vasculitis, retinitis, choroiditis, vascular occlusion, or hypotony
  - All Ixo-vec-related AEs were either mild or moderate
    - Most common Ixo-vec-related AEs[1] were dose-dependent anterior inflammation responsive to local corticosteroids and anterior pigmentary changes with no impact on vision
- Improved inflammatory profile observed with enhanced corticosteroid prophylaxis in LUNA as compared to OPTIC[2]
  - Oral prednisone did not demonstrate incremental benefit
  - IVT dexamethasone without difluprednate did not provide adequate prophylaxis
  - Local corticosteroid prophylaxis[3] was effective in minimizing inflammation with 91% of participants having no or minimal inflammation (0 or trace/0.5+ AC cells) at any study visit through Week 26

1. *Anterior chamber cell, anterior chamber pigmentation, iris transillumination defect, iritis*
2. *Khanani AM. Retina Society Annual Meeting Presentation 2021, Chicago, IL*
3. *Topical difluprednate with or without IVT dexamethasone (N=34)*

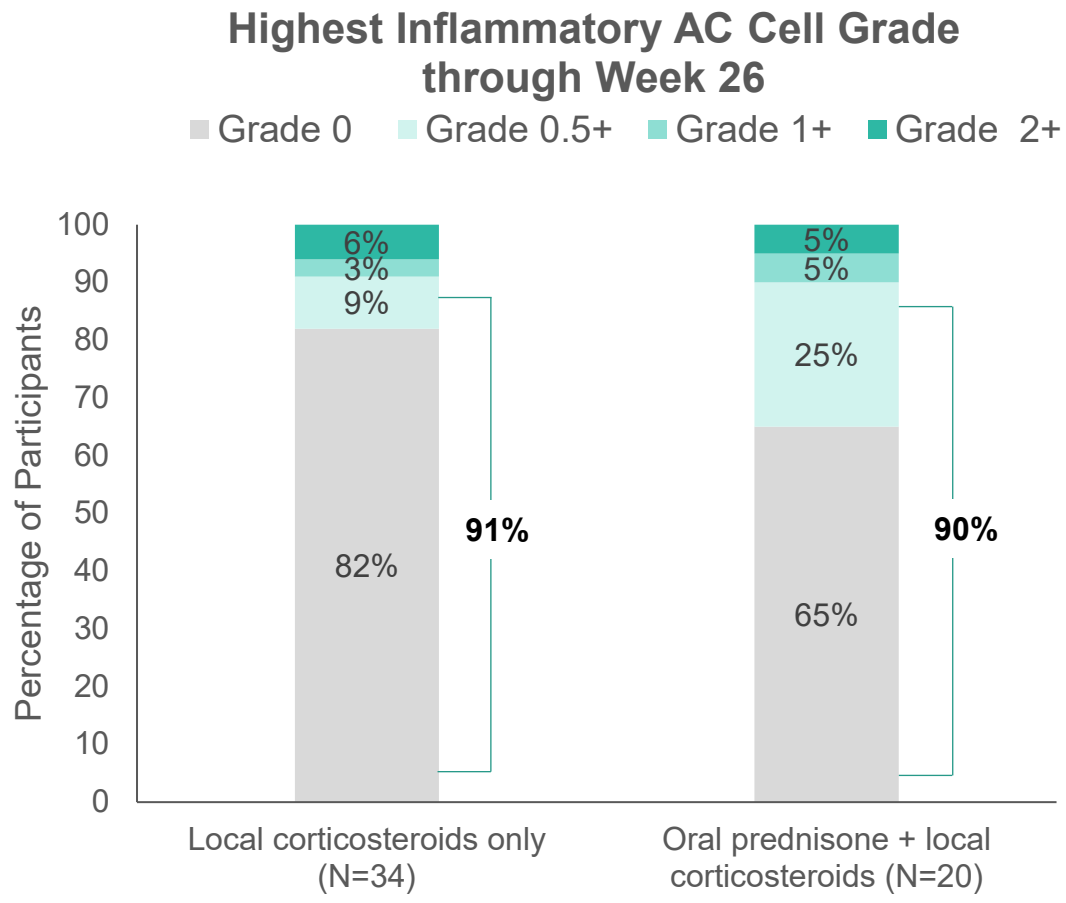
Data cut: 14Feb2024

Benefit of Enhanced Local Corticosteroid Prophylaxis Highlighted in LUNA Interim Analysis

Observed Benefit of Difluprednate Added to IVT Dexamethasone



No Observed Benefit of Oral Prednisone

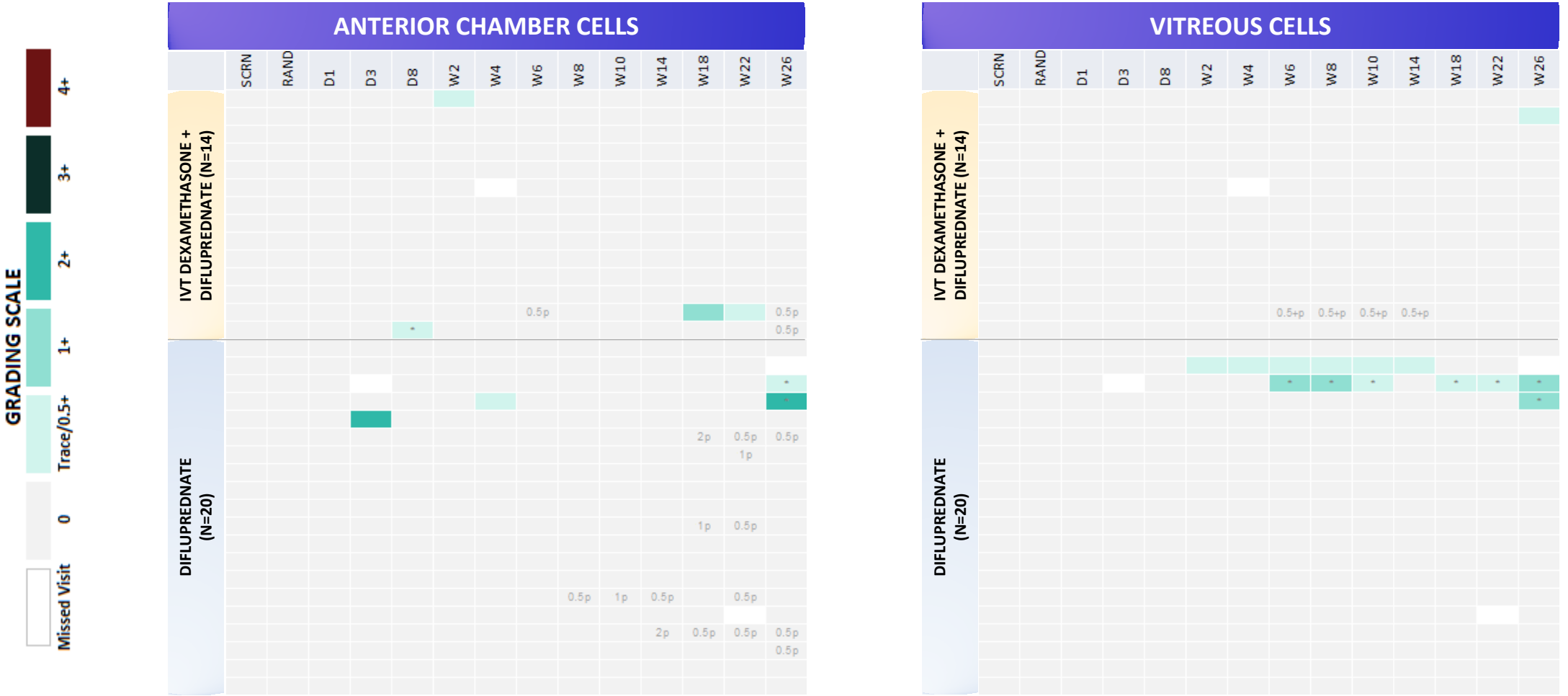


AC, anterior chamber. 100% pigmented cells excluded from analysis. Protocol amended early in study to include difluprednate after week 4 to match the taper in difluprednate regimens; if initiated after week 4 visit difluprednate may be adjusted at the discretion of investigator in consult with medical monitors (6 participants did not receive difluprednate topical as part of prophylaxis). 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: 14Feb2024

Local Corticosteroid Prophylaxis Regimens were Effective in Minimizing Inflammation

Interim LUNA data indicate that ocular inflammation is primarily located in anterior chamber and is responsive to local corticosteroids



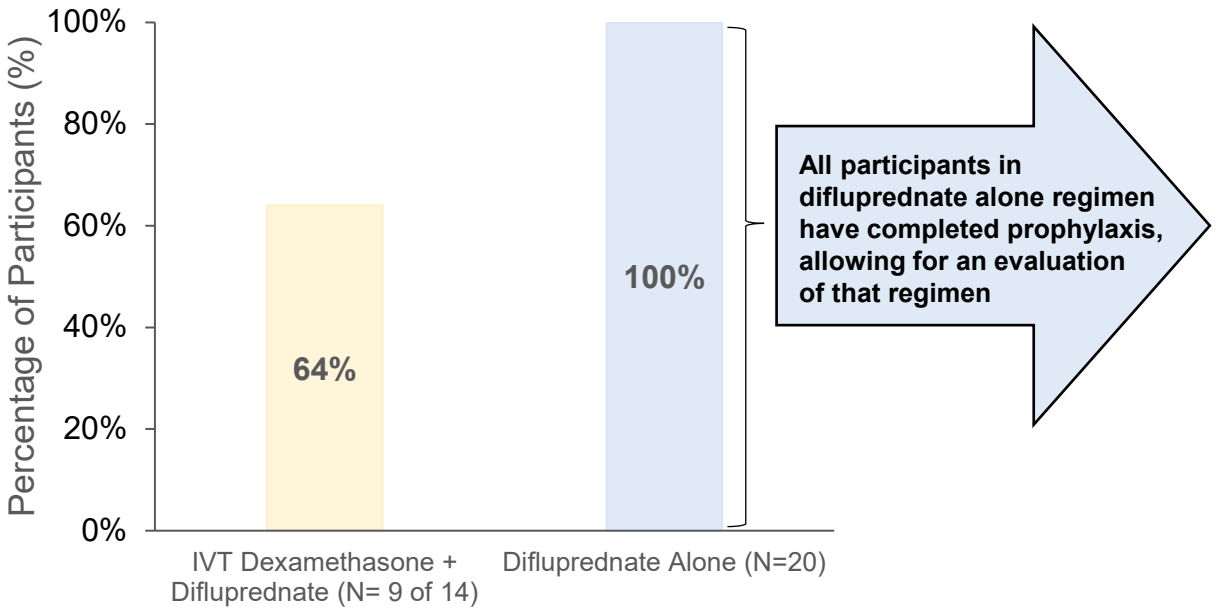
*Doses pooled in heatmaps to preserve investigator masking in an ongoing double masked study. *Mixed pigmented and non-pigmented cells are graded with the same color scheme and scale as non-pigmented cells.*
p, pigmented cell. Cell grades as assessed by slit lamp; grade categories are based on the Standardization 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

In the Difluprednate Alone Regimen, Inflammation was Dose Dependent and Responsive to Topical Corticosteroids

Local Corticosteroid Prophylaxis Arms (N=34)

Proportion of Participants Who Completed Prespecified Prophylactic Regimen at Week 26



Not all participants had completed prophylaxis at week 26 due to amended protocol regimens starting prophylaxis after week 4

Difluprednate Alone Prophylaxis Arms (N=20)

Participants, n	Ixo-vec $6x10^{10}$ vg/eye N = 10	Ixo-vec $2x10^{11}$ vg/eye N = 10
AC Cell Grade at Week 26		
0.5+	1	0
1+	0	0
2+	0	1
Anterior pigment-related AEs through Week 26		
Mild	3	2
Moderate	1	3

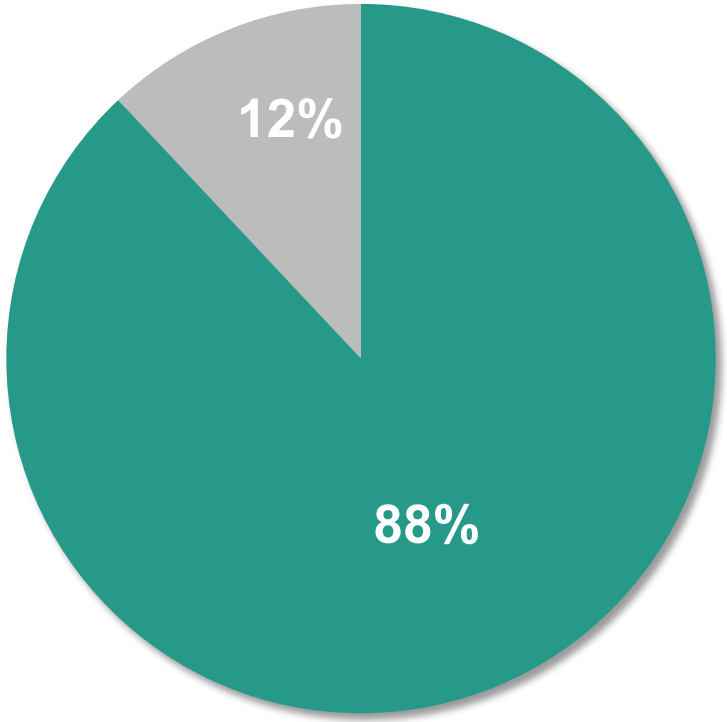
- No participants in the $6x10^{10}$ vg/eye dose cohort received corticosteroids for treatment of AC/V cells beyond the taper
- Topical difluprednate effectively managed AC/V cells when present in the $2x10^{11}$ vg/eye dose cohort
- Pigment-related AEs have had no impact on vision

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.

Data cut: 14Feb2024

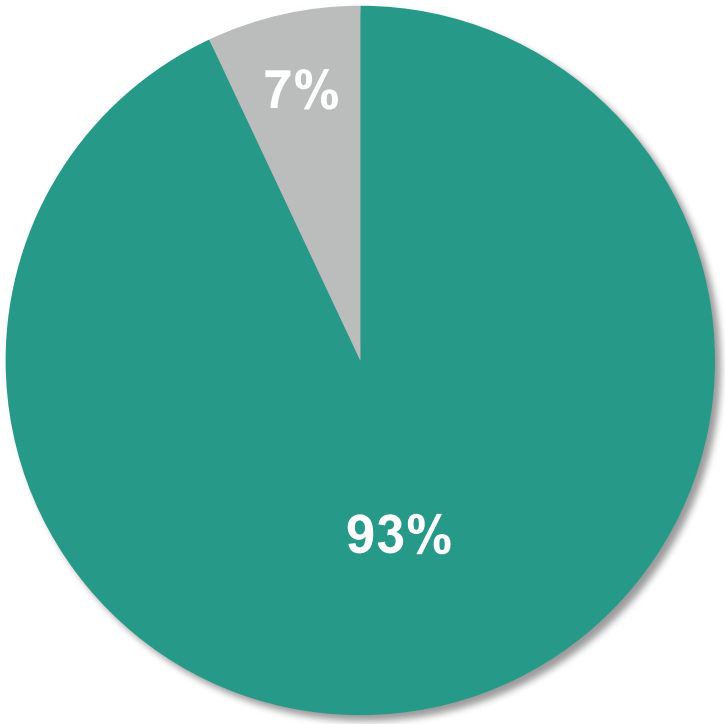
88-93% of LUNA Participants Prefer Ixo-vec in the Prespecified Patient Preference Survey

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

Data cut: 14Feb2024

LUNA 26-week Interim Analysis Key Takeaways

Efficacy

- Visual and anatomic outcomes were maintained through 26 weeks at both Ixo-vec doses of $6x10^{10}$ and $2x10^{11}$ vg/eye
- Substantial treatment burden reduction observed in patients previously requiring ≥10 annualized anti-VEGF injections:
  - ≥ 90% reduction in annualized anti-VEGF injections at both doses
  - 76% and 83% of patients remain free of injections at 6 months at the $6x10^{10}$ and $2x10^{11}$ doses, respectively

Safety

- Ixo-vec was well tolerated at both doses, $6x10^{10}$ and $2x10^{11}$ vg/eye, with no Ixo-vec-related serious adverse events
- Local corticosteroid prophylaxis[1] was effective in minimizing inflammation, with >90% of participants having no or minimal inflammation[2] through Week 26

Patient Preference

- 88% of LUNA participants prefer Ixo-vec over the previous anti-VEGF therapy they received for treatment of nAMD

LUNA is ongoing with analysis of the primary efficacy and safety endpoints to be performed at Week 52

1. *Topical difluprednate with or without IVT dexamethasone*
2. *0 or trace/0.5+ AC cells*

Data cut: 14Feb2024

Acknowledgements: LUNA Study Participants, Investigators, and Study Teams

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, PhD

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