UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 6-K

REPORT OF FOREIGN ISSUER
PURSUANT TO RULE 13a-16 OR 15d-16
OF THE SECURITIES EXCHANGE ACT OF 1934

For the month of September 2024

Commission File No. 001-39621

OPTHEA LIMITED
(Translation of registrant's name into English)

Level 4
650 Chapel Street
South Yarra, Victoria, 3141
Australia
(Address of registrant's principal executive office)

Indicate by check mark whether the registrant files or will file annual reports under cover Form 20-F or Form 40-F.
Form 20-F ☒ Form 40-F ☐

EXHIBIT INDEX

Exhibit	Description
99.1	**Press Release - Euretina Symposium**

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereto duly authorized.

OPTHEA LIMITED
(Registrant)

By: /s/ Frederic Guerard
Name: Frederic Guerard
Title: Chief Executive Officer

Date: 09/26/2024

Exhibit 99.1

EURetina Symposium 2024

Improving on the Standard of Care in nAMD:

Addressing the VEGF-C and -D Pathways

Sponsored by OPTHEA

Introduction and Objectives

Speaker: Arshad Khanani, MD, MA, FASRS

Dr. Arshad Khanani's Disclosures

- Consultant: AbbVie, Adverum, Alcon, Amgen, Annexin, Annexon, Apellis Pharmaceuticals, Aviceda Therapeutics, Beacon Therapeutics, Clearside Biomedical, Complement Therapeutics, 4DMT, Exegenesis, EyePoint Pharmaceuticals, Frontera 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
- Research support: Aviceda, Adverum, Alexion, Annexon, Apellis Pharmaceuticals, Aviceda Therapeutics, 4DMT, EyePoint, Exegenesis, Genentech, Gyroscope Therapeutics, Iveric Bio, Janssen, Kodiak, Neurotech, Ocular Therapeutix, Oxular, Regenxbio
- Stock options: Aviceda Therapeutics, Oculis, Opthea, PolyPhotonix, Recens Medical, Perfuse, RevOpsis, and Vial

Agenda

Time	Topic	Presenter/Moderator
1:00-1:05 pm	**Introduction and Objectives**	Chair: Arshad Khanani, MD, MA, FASRS
1:05-1:20 pm	**nAMD: Where Are We Today?** • Disease overview	Adnan Tufail, MD, MBBS, FRCOphth
1:20-1:35 pm	**Most Recent and Emerging Treatments in nAMD** • Treatment objectives for innovation in nAMD • Review of most recent treatments • Review of emerging treatments in phase 3 • An introduction to sozinibercept, a novel anti-VEGF-C & -D inhibitor	Gemmy Cheung, MD, MBBS, FRCOphth, FAMS, MC
1:35-1:50 pm	**Sozinibercept (OPT-302): An Emerging Therapy With the Potential to Raise the Standard-of-Care Benchmark in Visual Outcomes** • Phase 2b trial results • Phase 3 trials: COAST and ShORe	Anat Loewenstein, MD, MHA
1:50-2:00 pm	**Panel Discussion, Questions, Summary, and Closing Remarks**	Anat Loewenstein, MD, MHA

Objectives

1. Understand the role of VEGF-C and VEGF-D in nAMD
2. Establish that emerging therapies are focused primarily on reducing treatment burden (durability)
3. Introduce sozinibercept as the only late-stage emerging therapy that has the potential to improve standard of care in visual outcomes

Featured Speakers

Arshad Khanani, MD, MA, FASRS

Sierra Eye Associates
Managing Partner,
Director of Clinical Research,
Director of Fellowship

University of Nevada, Reno School of Medicine
Clinical Professor

Adnan Tufail, MD, MBBS, FRCOphth

Moorfields Eye Hospital, Medical Retina Service
Consultant Ophthalmologist

University College London
Professor

Gemmy Cheung, MD, MBBS, FRCOphth, FAMS, MC

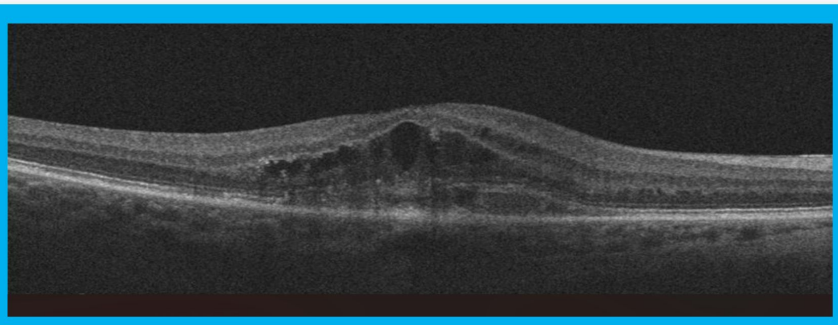
DukeNUS Medical School, Centre for Clinician-Scientist Development
Professor

Anat Loewenstein, MD, MHA

Tel Aviv Sourasky Medical Center
Deputy Director of Ambulatory Services, Head of Ophthalmology

Tel Aviv University, Medical School at the Sackler Faculty of Medicine
Professor of Ophthalmology and Vice Dean

Audience Question:
What Is Your Initial Treatment for This Patient?



Day 0 (Baseline):

BCVA = 59 letters
CST = 462 µm

A	B	C	D	E
Bevacizumab	Ranibizumab	Aflibercept 2 mg	Aflibercept 8 mg	Faricimab

nAMD: Where Are We Today?

Speaker: Adnan Tufail, MD, MBBS, FRCOphth

Dr. Adnan Tufail's Disclosures

- Consultant: AbbVie, Adverum, Annexon, Apellis Pharmaceuticals, Aviceda Therapeutics, Boehringer Ingelheim, EyePoint Pharmaceuticals, Genentech-Roche, Iveric Bio, Janssen Pharmaceuticals, Nanoscope, Novartis, Ocular Therapeutix, Opthea, Oxurion, Regenxbio, Thea Pharma

Objectives

1. Establish the impact of nAMD on quality of life
2. Review the evolution of current nAMD treatments
3. Establish the role of VEGF-C and VEGF-D in nAMD

Vision Impairment Negatively Impacts Independence and Quality of Life

- Mobility[1]
- Phone/ Computer Use[1,2*]
- Shopping[1,3*]
- Housekeeping[1-3*]
- Face Recognition[4]
- Driving/ Transportation Management[1,3,4*]
- Rx Management[1,3*]
- Laundry[1,2,5*]
- Reading[4]
- Cooking[1*]
- Finance Management[1-3*]

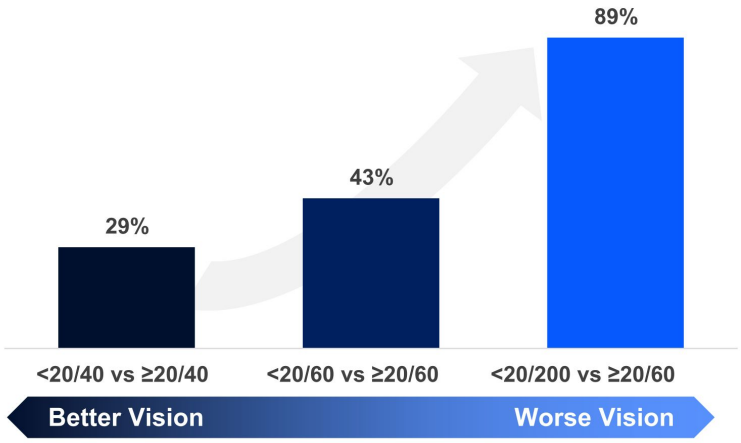
1 in 4 adults with vision loss report depression or anxiety[6]

*Instrumental activity of daily living.

1. Hochberg C, et al. Invest Ophthalmol Vis Sci. 2012;53:3201-3206. 2. Christ SL, et al. JAMA Ophthalmol. 2014;132(12):1400-1406. 3. Remillard ET, et al. Gerontologist. 2024;64(6):gnad169. 4. Sahel J-A, et al. Arch Ophthalmol. 2007;125(7):945-951. 5. Guo HJ, et al. (2022, Nov 14). In StatPearls. StatPearls Publishing. Retrieved Sep 10, 2024 from https://www.ncbi.nlm.nih.gov/books/NBK553126/. 6. Lundeen EA, et al. Ophthalmic Epidemiol. 2022;29(2):171-181.

Loss of Vision Leads to Increased Mortality Risk

Hazard for All-Cause Mortality[1]
Higher in People With Vision Impairment



Decrease of 1 ETDRS letter per year increases mortality risk by 16%[2]
associated exclusively with IADL levels

ETDRS, Early Treatment Diabetic Retinopathy Study; IADL, instrumental activities of daily living.
1. Erlich JR, et al. Lancet Glob Health. 2021;9:e418-e430. 2. Christ SL, et al. JAMA Ophthalmol. 2014;132(12):1400-1406.

Evolution of nAMD Treatments to Today

Verteporfin[1] — **2000**
Photosensitizing agent used in laser treatment

Improved efficacy[2,3]

MACUGEN (PEGAPTANIB SODIUM INJECTION) — **2004**
Targets isoform-specific VEGF-A_{165} inhibition[4]

LUCENTIS (RANIBIZUMAB INJECTION), AVASTIN (bevacizumab) — **2006**
Targets all isoforms of VEGF-A[5,6*]

EYLEA (aflibercept) Injection For Intravitreal Injection — **2011**
Targets VEGF-A, VEGF-B, & PIGF[6,7]

Beovu (brolucizumab-dbll) Injection — **2019**
Targets all isoforms of VEGF-A[8]

SUSVIMO ranibizumab injection 100 mg/mL For Ocular Implant — **2021**
Targets all isoforms of VEGF-A[9,10]

VABYSMO faricimab-svoa injection 6 mg — **2022**
Targets VEGF-A & Ang-2[11]

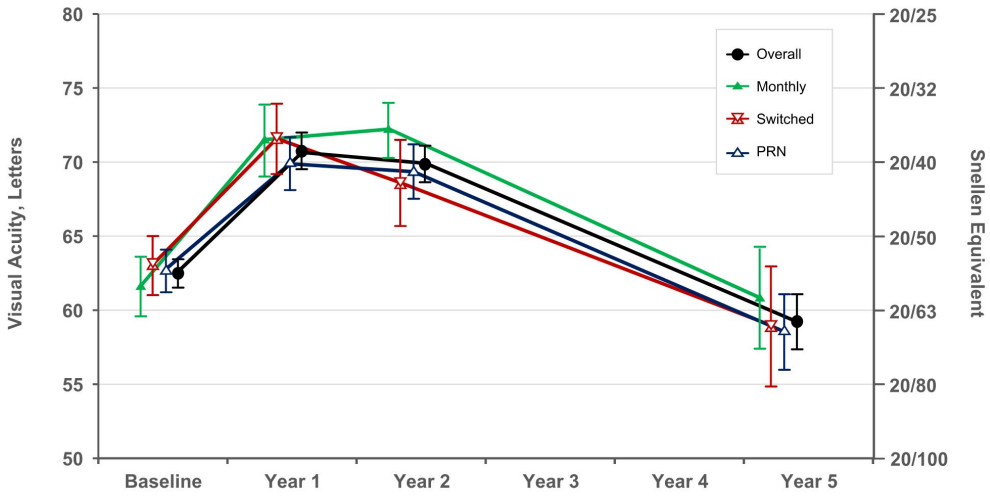
EYLEA HD (aflibercept) Injection 8 mg — **2023**
Targets VEGF-A, VEGF-B, & PIGF[6,12,13]

- Early treatments such as veteporfin/PDT used light sensitivity to break down blood vessels in the eye[1]
- Pegaptanib was the first drug to the VEGF pathway by inhibiting the 165 isoform of VEGF[4]
- Since then, developing treatments have all targeted the VEGF pathway, specifically VEGF-A[6]
- Despite attempts at improving treatment results, we are not seeing real-world superiority over previous treatments[6]

*Avastin (bevacizumab) used off-label. Ang-2, angiopoietin-2; nAMD, neovascular age-related macular degeneration; PDT, photodynamic therapy; PIGF, placental growth factor; VEGF, vascular endothelial growth factor. 1. VISUDYNE [prescribing information]. Charleston, SC: Bausch & Lomb Incorporated. https://www.bausch.com/globalassets/pdf/packageinserts/pharma/visudyne-prescribing-information.pdf. Revised Feb 2023. 2. Brown DM, et al. N Engl J Med. 2006;355:1432-1444. 3. Nowak MS, et al. Med Sci Monit. 2012;18(6):CR374-380. 4. MACUGEN [prescribing information]. San Dimas, CA: Gilead Sciences, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021756s018lbl.pdf. Revised Jul 2011. 5. LUCENTIS [prescribing information]. South San Francisco, CA: Genentech, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125156s128lbl.pdf. Revised Feb 2024. 6. Khachigian LM, et al. J Transl Med. 2023;21(1):133. 7. EYLEA [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc. https://www.regeneron.com/downloads/eylea_fpi.pdf. Revised Dec 2023. 8. BEOVU [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. https://www.novartis.com/us-en/sites/novartis_us/files/beovu.pdf. Revised Jul 2024. 9. SUSVIMO [prescribing information]. South San Francisco, CA: Genentech, Inc. https://www.gene.com/download/pdf/susvimo_prescribing.pdf. Revised Apr 2022. 10. Genentech: Press Release. Oct 22, 2021. https://www.gene.com/media/press-releases/14935/2021-10-22/fda-approves-genentechs-susvimo-a-first- 11. VABYSMO [prescribing information]. South San Francisco, CA: Genentech, Inc. https://www.gene.com/download/pdf/vabysmo_prescribing.pdf. Revised Jul 2024. 12. EYLEA HD [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc. https://www.regeneron.com/downloads/eyleahd_fpi.pdf. Revised Dec 2023. 13. Regeneron: Press Release. Aug 18, 2023. https://investor.regeneron.com/news-releases/news-release-details/eylea-hd-aflibercept-injection-8-mg-approved-fda-treatment-wet. All websites accessed Sep 11, 2024.

Overview of Current Anti-VEGF Therapies

Half of CATT follow-up study patients had visual acuity worse than 20/40 at 5 years

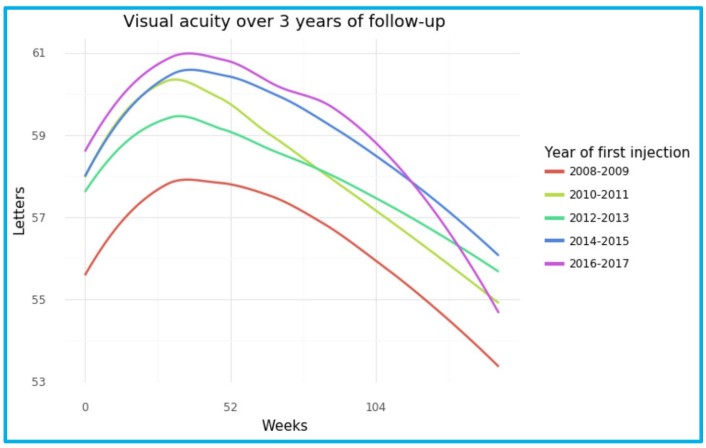


CATT, Comparison of Age-Related Macular Degeneration Treatments Trials; PRN, as needed; VEGF, vascular endothelial growth factor.
CATT Research Group, et al. Ophthalmology. 2016;123(8):1751-1761.

Effect of Treatment Paradigm Change in nAMD on Outcomes

Based on results from a 12-year follow-up of 42,161 patients[1,2]

Group (n)	Number of injections (mean ± SD)	Number of visits (mean ± SD)	Visit/injection ratio (median)
2016–2017 (633)	11.2 ± 6.1	24.2 ± 7.3	2.17
2014–2015 (6,083)	10.4 ± 6.1	22.5 ± 7.9	2.20
2012–2013 (5,432)	7.9 ± 5.1	21.9 ± 8.2	3
2010–2011 (5,017)	9.3 ± 5.6	23.4 ± 9.9	2.6
2008–2009 (2,395)	9.5 ± 5.8	24.4 ± 11.2	2.71



- Baseline VA improved over the years—patients identified earlier
- Final VA improved over the years
- Trend is the same—patients are still losing vision over time despite the move to more “advanced” treatment regimens

- In a multivariable analysis accounting for baseline VA, which improved over the years, **year of treatment initiation was not related to better outcomes**
- Baseline VA remains strongly associated with outcome

nAMD, neovascular age-related macular degeneration; VA, visual acuity.

1. Schwartz R. Ophthalmol Retina. 2021;5(8):e11-e22. 2. Data on file.

Advantages and Limitations of Current Anti-VEGF-A Therapies

Advantages

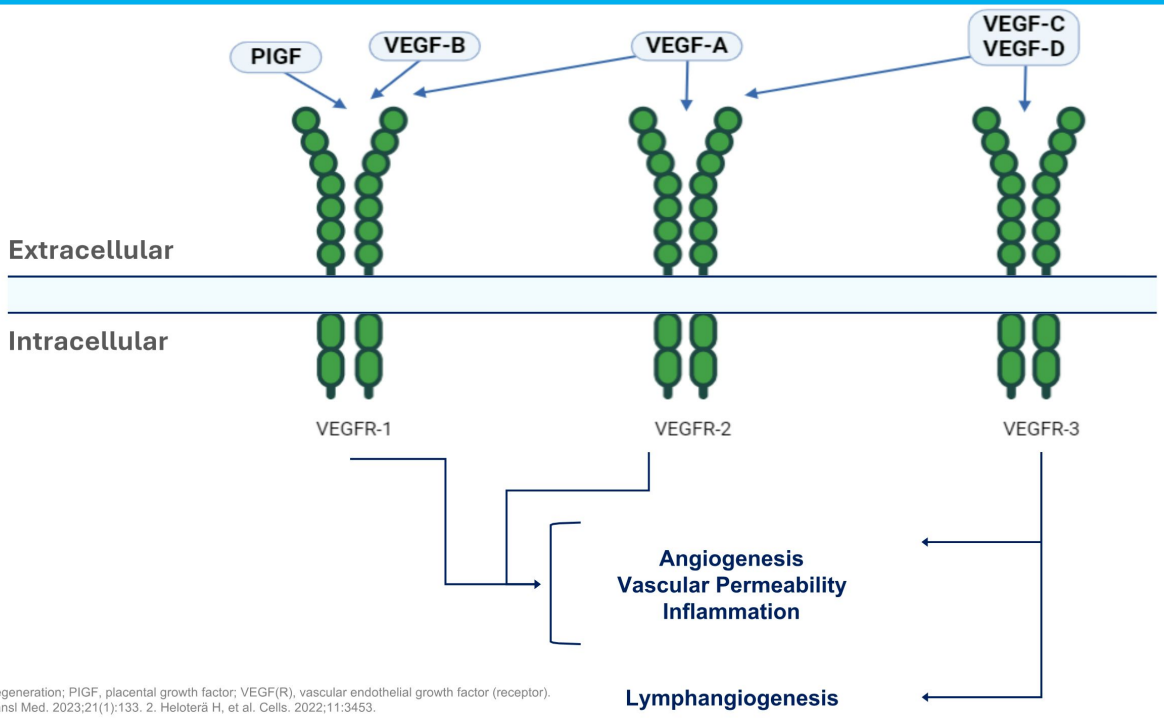
- Improved quality of life[1]
- Visual gains[1]
- Multiple anti-VEGF drugs available[2]
- Favorable safety profile[1,3]
- Clinical trial evidence[2]

Limitations

- **Continued limitations on visual outcomes from all current therapies[4]**
- **Suboptimal responses with current anti-VEGF therapies in 25–35% of patients with nAMD[1]**
- **Further vision loss at 12+ months for 25% of patients treated with anti-VEGFs[4]**
- **Real-world evidence does not match clinical trial data[5]**
- **Persistent macular fluid in 60% of patients with nAMD[2]**
- **Frequent treatment required to maintain vision[1]**

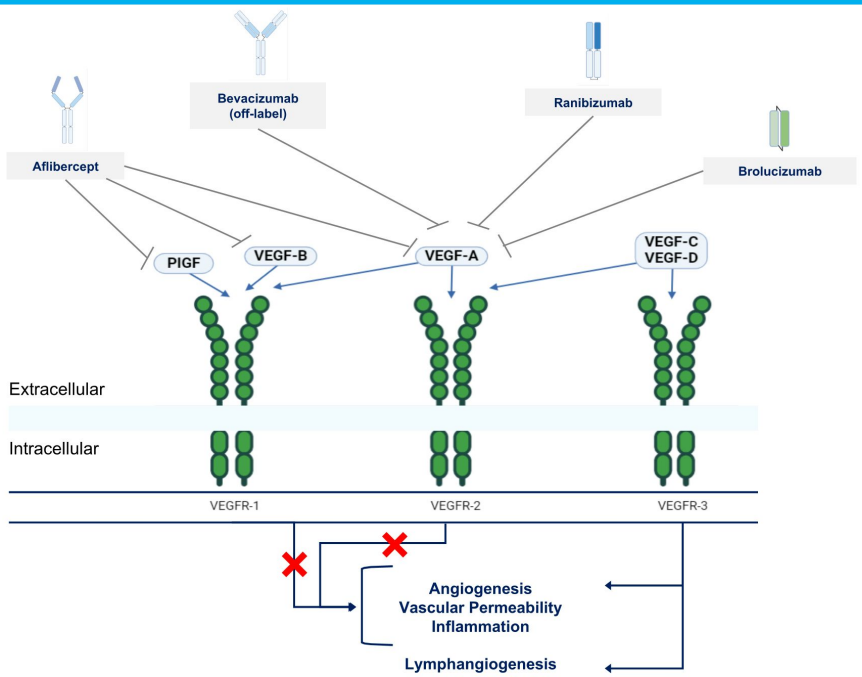
PCV, polypoidal choroidal vasculopathy with branching vascular network; PDA, persistent disease activity; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor. 1. Khachigian LM, et al. J Transl Med. 2023;21(1):133. 2. Mettu PS, et al. Prog Retin Eye Res. 2021;82:100906. 3. Heier JS, et al. Ophthalmology. 2012;119(12):2537-2548. 4. Garweg JG, et al. Graefes Arch Clin Exp Ophthalmol. 2018;256(4):823-831. 5. Data on file.

Pathophysiology of AMD and the Role of VEGF-A[1,2]



AMD, age-related macular degeneration; PIGF, placental growth factor; VEGF(R), vascular endothelial growth factor (receptor).
1. Khachigian LM, et al. J Transl Med. 2023;21(1):133. 2. Heloterä H, et al. Cells. 2022;11:3453.

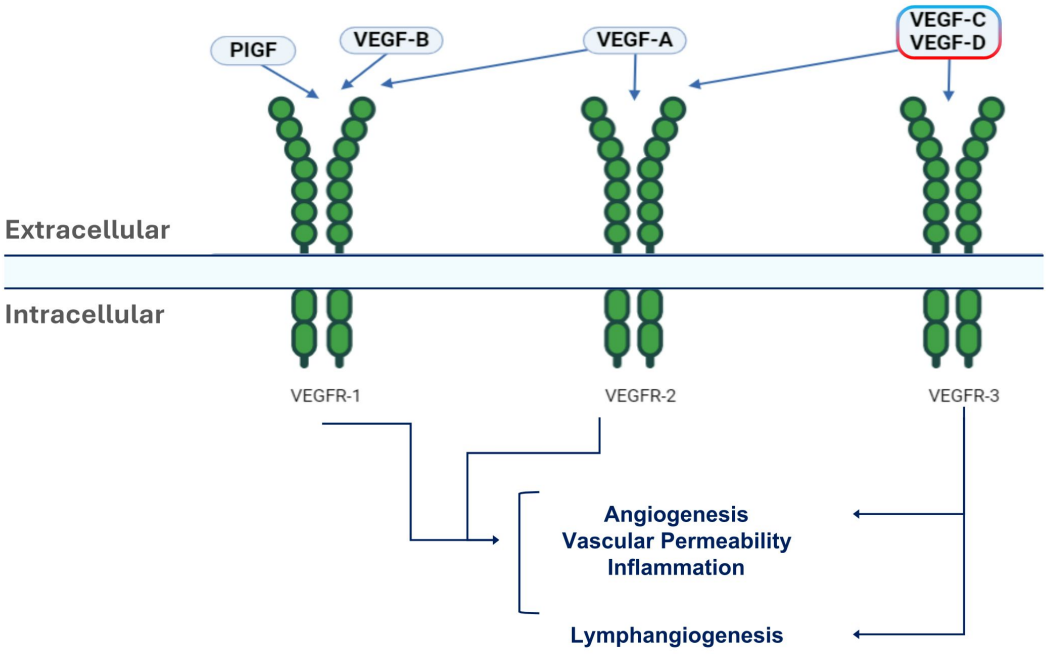
The Role of Anti-VEGF Inhibitors in nAMD[1-3]



- Current anti-VEGF therapies primarily target VEGF-A but do not target VEGF-C and VEGF-D[1]
- VEGF-C and D promote angiogenesis and vascular leakage[2]

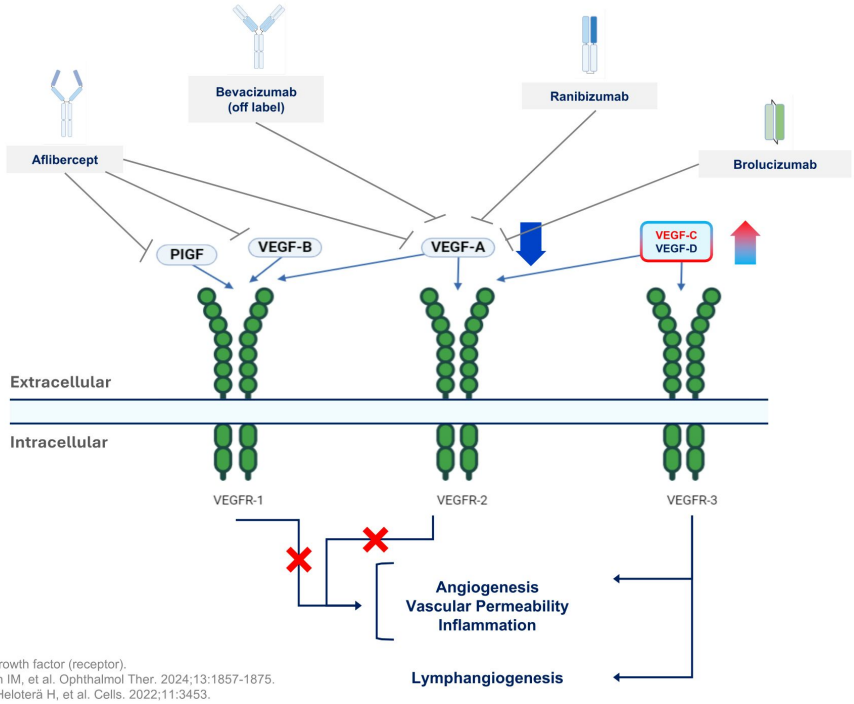
nAMD, neovascular age-related macular degeneration; PlGF, placental growth factor; VEGF(R), vascular endothelial growth factor (receptor). 1. Khachigian LM, et al. J Transl Med. 2023;21(1):133. 2. Jackson TL, et al. Ophthalmology. 2023;130(6):588-597. 3. Heloterä H, et al. Cells. 2022;11:3453.

VEGF-C and VEGF-D Are Upregulated Following VEGF-A Inhibition in nAMD[1-3]



nAMD, neovascular age-related macular degeneration; PIGF, placental growth factor; VEGF(R), vascular endothelial growth factor (receptor).1. Khachigian LM, et al. J Transl Med. 2023;21(1):133. 2. Leitch IM, et al. Ophthalmol Ther. 2024;13:1857-1875. 3. Heloterä H, et al. Cells. 2022;11:3453.

VEGF-A Inhibition Leads to Upregulation of VEGF-C[1-4]



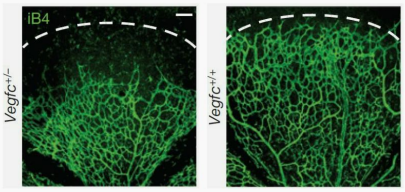
PIGF, placental growth factor; VEGF(R), vascular endothelial growth factor (receptor).

1. Khachigian LM, et al. J Transl Med. 2023;21(1):133. 2. Leitch IM, et al. Ophthalmol Ther. 2024;13:1857-1875.
3. Jackson TL, et al. Ophthalmology. 2023;130(6):588-597. 4. Heloterä H, et al. Cells. 2022;11:3453.

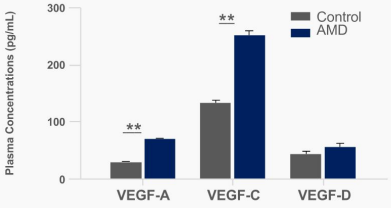
Role of VEGF-C/D in nAMD

Published Data Suggest VEGF-C/D May Contribute to Suboptimal Responses to Anti-VEGF-A Therapy

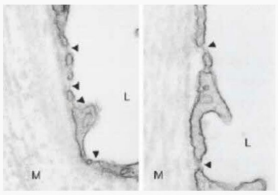
VEGF-C Stimulates Retinal Angiogenesis[1]



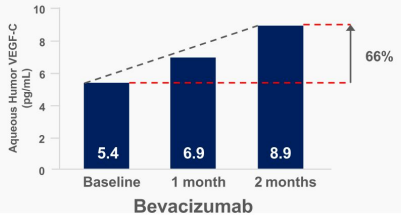
Circulating VEGF-C Levels Significantly Elevated in AMD Patients[3]



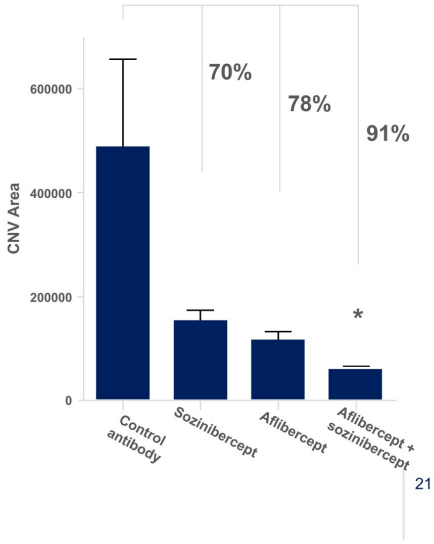
VEGF-A and VEGF-C Induce Vascular Leakage/Permeability[2]



Elevated VEGF-C in Aqueous Humor Following Anti-VEGF-A Therapy in Patients With nAMD[3]



Additive Benefit of VEGF-A and VEGF-C/D Inhibition in Mouse nAMD Model[3]

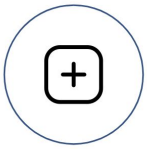


(n)AMD, (neovascular) age-related macular degeneration; CNV, choroidal neovascularization; VEGF, vascular endothelial growth factor.

1. Tammela T, et al. Nat Cell Biol. 2011;13(10):1202-1213. 2. Cao R, et al. Circ Res. 2004;94:664-670. 3. Data on file.

Summary and Conclusion

Current nAMD therapies primarily target VEGF-A[1]



nAMD is multifactorial, and targeting only VEGF-A may contribute to suboptimal response[1]

Elevated levels of VEGF-C/D leads to angiogenesis and vascular leakage[2]

Conclusion:
There is still unmet need for further visual improvements in the treatment of nAMD

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.
1. Khachigian LM, et al. J Transl Med. 2023;21(1):133. 2. Jackson TL, et al. Ophthalmology. 2023;130(6):588-597.

Most Recent and Emerging Treatments in nAMD

Speaker: Gemmy Cheung, MD, MBBS, FRCOphth, FAMS, MC

Dr. Gemmy Cheung's Disclosures

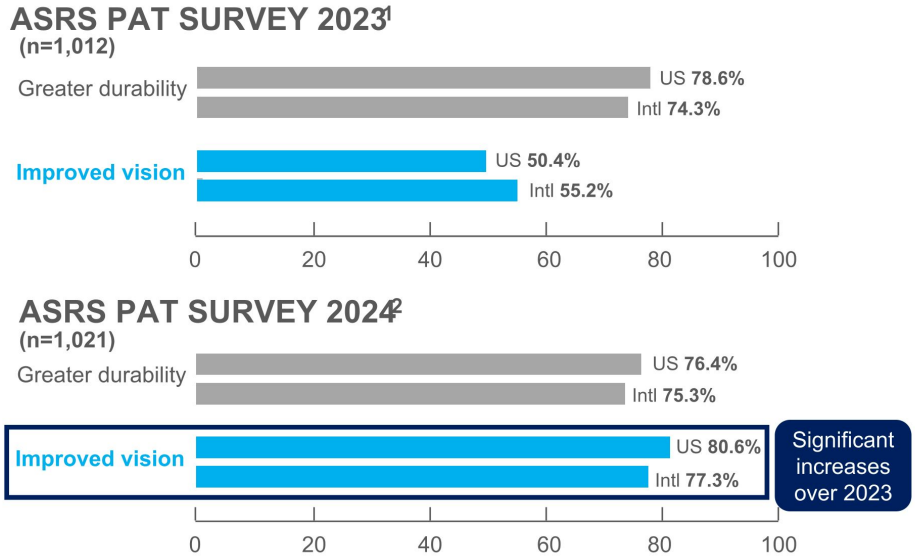
- Consultant: Avirmax, Astellas, Bayer, Boehringer Ingelheim, Janssen, Novartis, Opthea, Roche, Topcon, Zeiss

Objectives

1. Evaluate treatment objectives for innovation in nAMD
2. Review recently approved treatments in nAMD
3. Explore emerging treatments in nAMD

Improved Vision Is Now the Greatest Unmet Need for nAMD

What are the greatest unmet needs in treating wet AMD and DME?



Goals of Anti-VEGF Treatment

- **Optimal** visual improvements
- **Maintenance** of visual gain
- **Less frequent** dosing
- **Fewer** follow-up visits
- **Low rate** of AEs

ASRS, American Society of Retinal Specialists; DME, diabetic macular edema; Intl, international; nAMD, neovascular age-related macular degeneration; PAT, Preferences and Trends; VEGF, vascular endothelial growth factor.

1. Hahn P, ed. ASRS 2023 Preferences and Trends Membership Survey. Chicago, IL. American Society of Retina Specialists; 2023. 2. Data on file.

Despite Treatment with Standard of Care Anti-VEGF-A Therapies, the Majority of Patients Achieve Suboptimal Vision Outcomes

Despite treatment with anti-VEGF-A therapy*:

>45% do not achieve significant vision gains[1]

>60% with have **persisting macular fluid**[2]

25% will have **further vision loss at 12+ months**[3]

The majority[2] of patients **fail to achieve**

20/40 vision

Most patients

cannot resume

routine daily activities, such as driving or reading[4]

BCVA, best corrected visual acuity; CST, central subfield thickness; PCV, polypoidal choroidal vasculopathy with branching vascular network; PDA, persistent disease activity; SD-OCT, spectral domain optical coherence tomography; VEGF, vascular endothelial growth factor. *Based on randomized controlled clinical trial data; >45% fail to achieve ≥2 lines improvement in BCVA; persisting fluid: SD-OCT CST ≥300 µM or time-domain OCT CST ≥250 µM.

1. Lux A, et al. Br J Ophthalmol. 2007;91:1318-1322. 2. Mettu PS, et al. Prog Retin Eye Res. 2021;82:100906. 3. Garweg JG, et al. Graefes Arch Clin Exp Ophthalmol. 2018;256(4):823-831. 4Data on file.

Current State of nAMD Treatments

- **Recently approved treatments reduce treatment burden but do not lead to superior visual gain**
- **Emerging therapies are targeting increased durability**

nAMD, neovascular age-related macular degeneration.

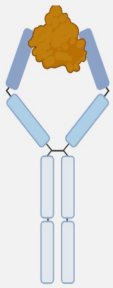
Aflibercept 8 mg, Faricimab 6 mg, and Port Delivery System with Ranibizumab Demonstrate Improved Durability Compared With Other Anti-VEGF Treatments

Aflibercept 8 mg[1,2]

Soluble decoy receptor fusion protein

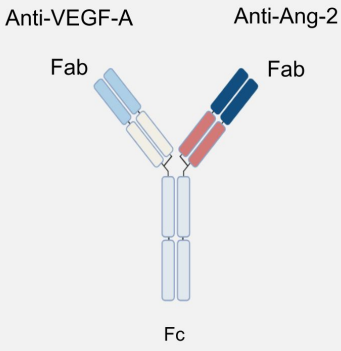
VEGF-A trap

Also targets VEGF-B and PlGF



Faricimab 6 mg[3]

Bispecific antibody



Ranibizumab implant[4,5]

Port delivery system

(not currently approved in EU)

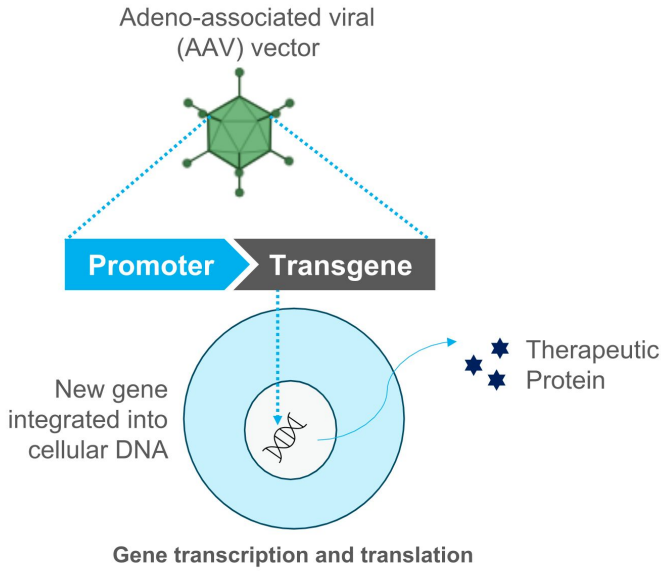
Non-inferior in vision gain compared to standard-of-care anti-VEGF therapies
Majority of patients maintained on 12- to 16-week dosing intervals[6]

Non-inferior in vision gain
Refillable every 24 weeks[4,5]

Aflibercept 8 mg is marketed as Eylea HD, Faricimab 8 mg is marketed as Vabysmo, Ranibizumab injection is marketed as Susvimo. Ang-2, angiopoietin-2; PlGF, placental growth factor; VEGF, vascular endothelial growth factor.1. EYLEA HD [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc. https://www.regeneron.com/downloads/eyleahd_fpi.pdf. Revised Dec 2023. 2. Heier JS, et al. Ophthalmology. 2012;119(12):2537-2548. 3. VABYSMO [prescribing information]. South San Francisco, CA: Genentech, Inc. https://www.gene.com/download/pdf/vabysmo_prescribing.pdf. Revised Jul 2024. 4. Holekamp NM, et al. Ophthalmology. 2022;129(3):295-307. 5. SUSVIMO [prescribing information]. South San Francisco, CA: Genentech, Inc. https://www.gene.com/download/pdf/susvimo_prescribing.pdf. Revised Apr 2022. 6. Heier JS, et al. Lancet. 2022;399(10326):729-740.

Emerging Therapy: Gene Therapy Shows Promise to Dramatically Reduce Treatment Burden

Uses non-integrating viral vector that encodes genetic material to make an anti-VEGF protein



Advantages[1]

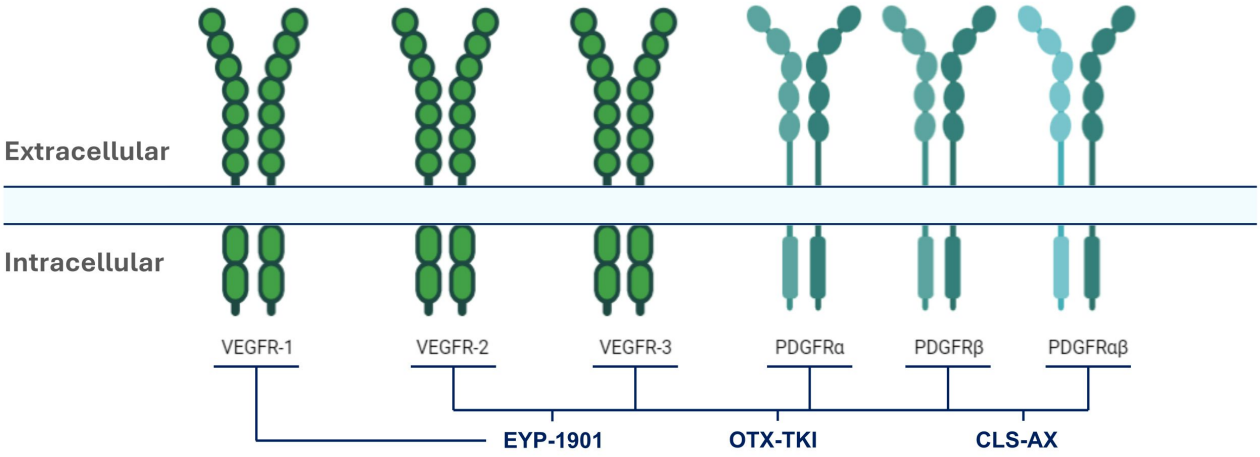
- Substantial reduction in treatment burden
- Potential for one-time treatment

Limitations[1,2]

- Prolonged corticosteroid prophylaxis (IVT administration) – cataract, ↑IOP
- Intraocular inflammation (IOI)
- Frequent IOI monitoring
- Potential for chronic uveitis
- Lack of long-term safety
- Potential cost

IOP, intraocular pressure; IVT, intravitreal; VEGF, vascular endothelial growth factor.
1. Khanani AM, et al. Eye. 2022;36:303-311. 2. Khanani AM, et al. eClinicalMedicine. 2024;67:102394.

Emerging Therapy: Tyrosine Kinase Inhibitors Work Intracellularly to Inhibit Downstream Effects of VEGF and PDGF

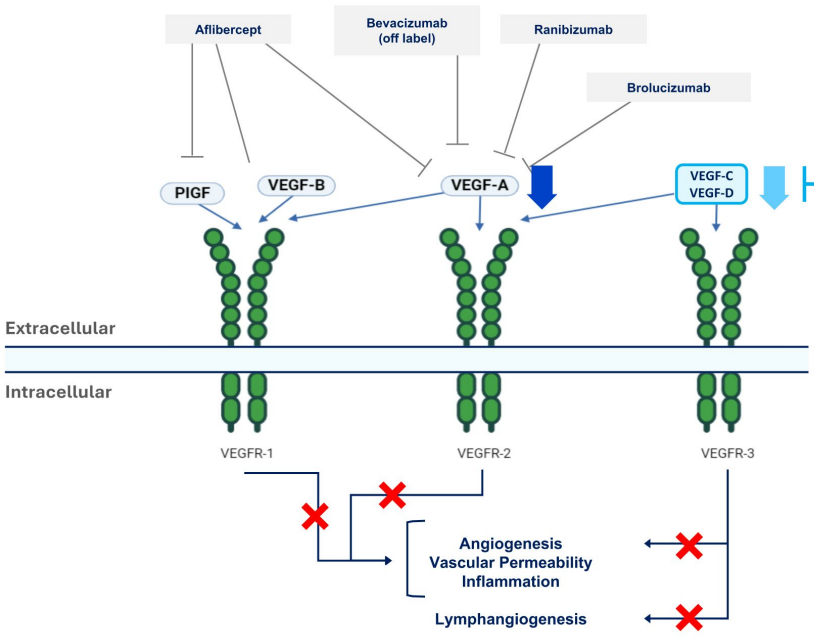


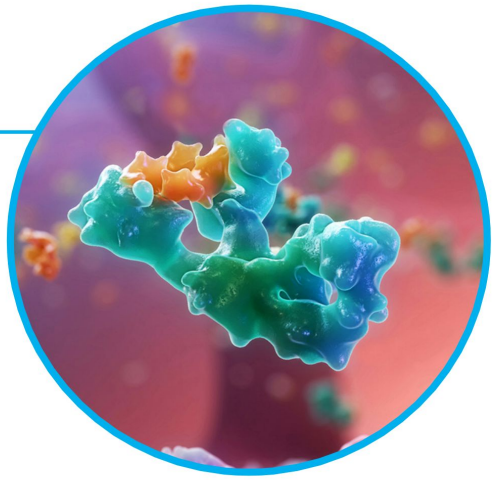
- OTX-TKI, EYP-1901, and CLS-AX are in clinical trials for treatment of nAMD[1-4]
- Potential for TKI sustained release to provide every-6-months dosing
- Targeting further reduction in treatment burden

PDGF(R), platelet-derived growth factor (receptor); TKI, tyrosine kinase inhibitor; VEGF(R), vascular endothelial growth factor (receptor).

1. Abbey AM, et al. Presented at ARVO 2023. 2. Patel S, et al. Ophthalmol Sci. 2024;4(5):100527. 3. Moshfeghi AA, et al. IOVS. 2022;64:936. 4. Barakat MR, et al. Ophthalmology Science. 2025;5(1):100586.

Sozinibercept Combination Therapy Achieves Broad Blockade of the Validated Pathway in nAMD[1-4]



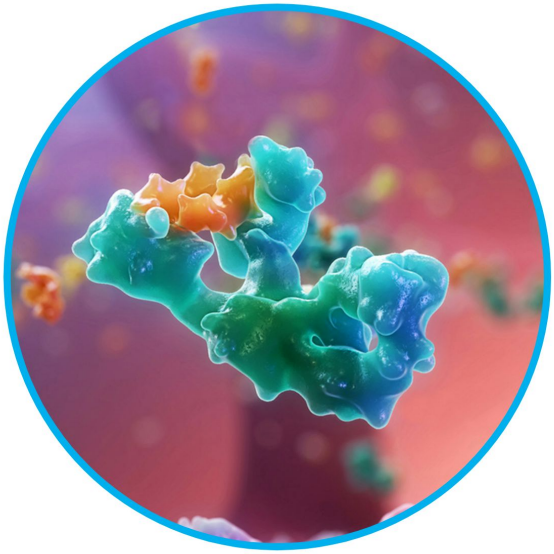


Sozinibercept
Fully Human Molecule

nAMD, neovascular age-related macular degeneration; PIGF, placental growth factor; VEGF(R), vascular endothelial growth factor (receptor).

1. Khachigian LM, et al. J Transl Med. 2023;21(1):133. 2. Jackson TL, et al. Ophthalmology. 2023;130(6):588-597. 3. Heloterä H, et al. Cells. 2022;11:3453. 4. Leitch IM, et al. Ophthalmol Ther. 2024;13:1857-1875.

Sozinibercept Is a Novel VEGF-C/D “Trap” Inhibitor[1]



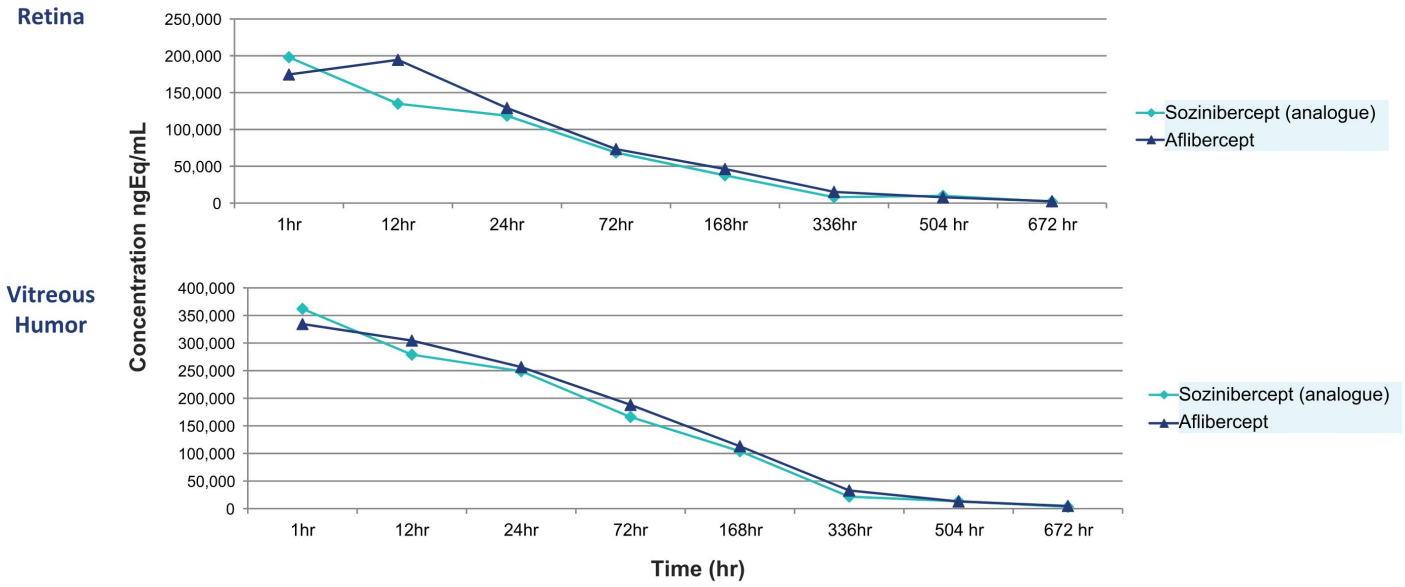
Sozinibercept
Fully Human Molecule

- A “trap” comprising the extracellular domains 1-3 of VEGFR-3 and the Fc fragment of IgG1
- Potent inhibitor of VEGF-C and VEGF-D
- 140 kDa
- Comparable ocular biodistribution and similar ocular pharmacokinetics to aflibercept 2 mg

Sozinibercept has characteristics to match extended dosing regimens and well-tolerated safety profiles of standard-of-care therapies

IgG, immunoglobulin G; VEGF(R), vascular endothelial growth factor (receptor). 1. Data on file.

Intravitreal Sozinibercept Has Similar Ocular Biodistribution & PK to Aflibercept - Potential for Similar Durability[1]



PK, pharmacokinetics. 1. Data on file.

Summary and Conclusion

- There continues to be great innovation in nAMD development
- Most potential new treatment are focused on durability, not on improved **VISUAL OUTCOMES** as standard of care

Objective: Better Durability[1,2]		Objective: Better Visual Outcomes[1]
Tyrosine kinase inhibitors	Gene therapy	
OTX-TKI	RGX-314	Sozinibercept
EYP-1901	4D-150	
CLS-AX	IXO-VEC	

Sozinibercept is the only late-stage drug in development targeting superior visual gain

nAMD, neovascular age-related macular degeneration.
1. Leitch IM, et al. Ophthalmol Ther. 2024;13:1857-1875. 2. Khanani AM, et al. eClinicalMedicine. 2024;67:102394.

Sozinibercept (OPT-302): An Emerging Therapy With the Potential to Raise the Standard-of-Care Benchmark in Visual Outcomes

Speaker: Anat Loewenstein, MD, MHA

Prof. Anat Loewenstein's Disclosures

- Head of Retina, Tel Aviv Medical Center; Vice President Tel Aviv Medical Center

- Consultant: Abbvie, Bayer Health Care, Beyeonics, Notal Vision, Novartis, Roche, Syneos, Ocular Therapeutics, Apellis, Oxurion, 4DMT, OcuTerra, Annexon, Astellas, J&J, Ocuphire Pharma, Opthea, Oculis, Alkeus, EyePoint

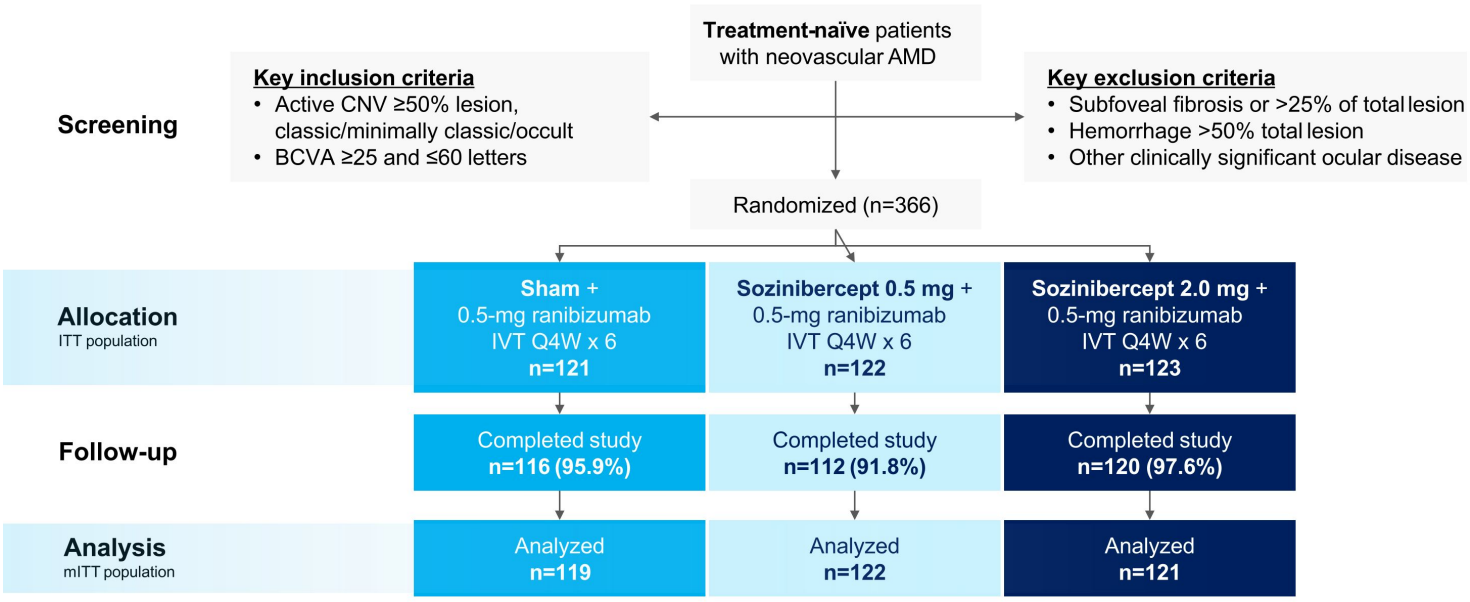
Objectives

1. Review Phase 2b Trial Results
2. Present Phase 3 Trials: COAST and ShORe

Phase 2b Trial Results

Speaker: Anat Loewenstein, MD, MHA

Phase 2b nAMD Trial Overview



BCVA, best corrected visual acuity; CNV, choroidal neovascularization; IVT, intravitreal; (m)ITT, (modified) intention to treat; nAMD, neovascular age-related macular degeneration; Q4W, once every 4 weeks; VA, visual acuity.
ITT population: all participants who were randomized into the study irrespective of whether study medication was administered; safety population: all participants in the ITT but excluding those who did not receive at least one dose of study medication; mITT population: all participants in the safety population but excluding any participant without a baseline VA score and/or any participant who did not return for at least one post-baseline visit.
Jackson TL, et al. Ophthalmology. 2023;130(6):588-597.

Phase 2b Primary and Secondary Endpoints

Primary Endpoint

Mean change from baseline in BCVA at Week 24

Key Secondary Endpoints

Proportion of patients gaining ≥15 letters (ETDRS) from baseline at Week 24

Change in CST from baseline at Week 24

Change in intraretinal and subretinal fluid from baseline to Week 24

Safety and tolerability

Select Prespecified Subgroups

Predominantly classic, minimally classic, & occult lesions (stratification factor)

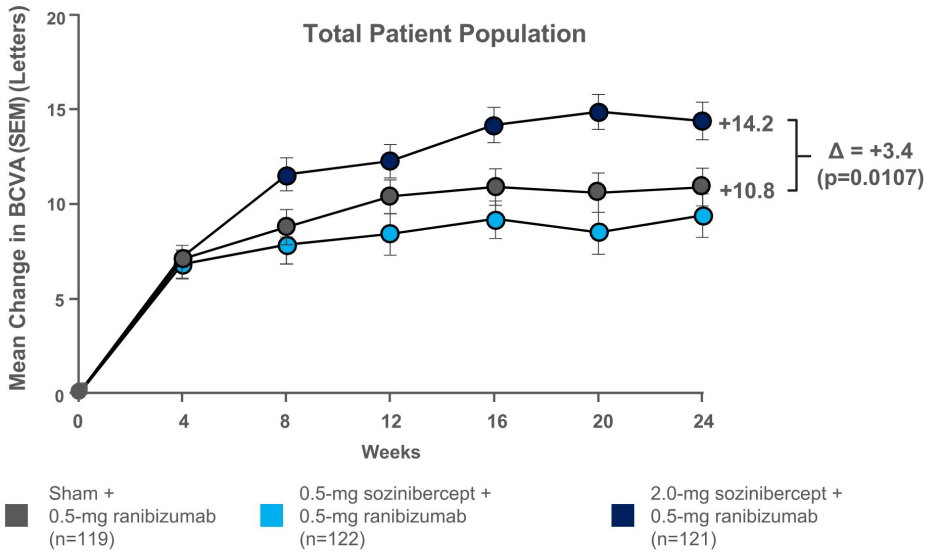
Retinal angiomatous proliferation (RAP) detected/not detected at baseline

Idiopathic polypoidal choroidal vasculopathy (PCV) detected/not detected at baseline

BCVA, best corrected visual acuity; CST, central subfield thickness; EDTRS, Early Treatment Diabetic Retinopathy Study.
Jackson TL, et al. Ophthalmology. 2023;130(6):588-597.

Sozinibercept Achieves Primary Clinical Trial Endpoint

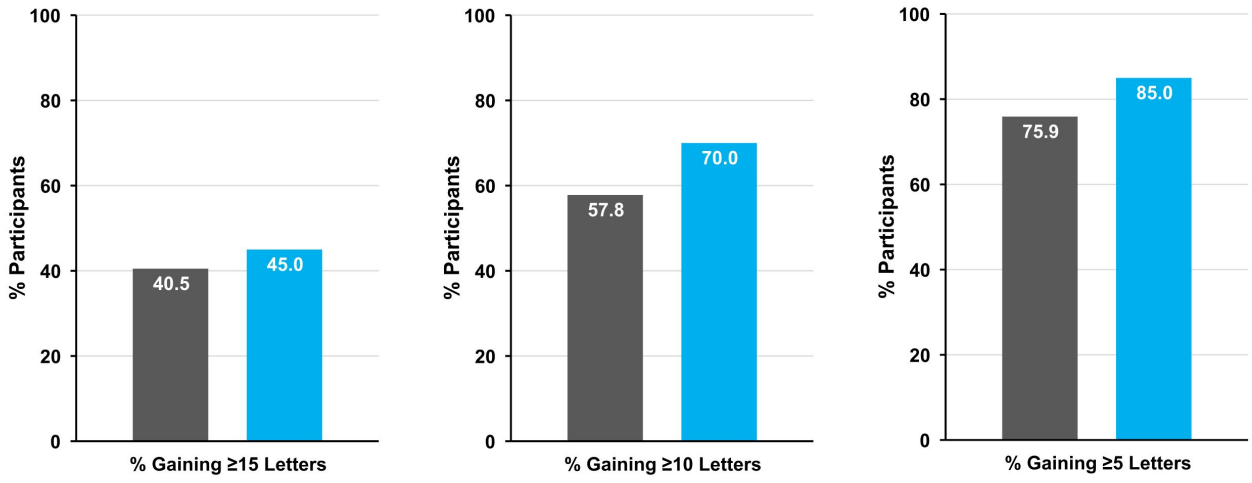
Phase 2b primary endpoint achieved[1,2]



BCVA, best corrected visual acuity; mITT, modified intention to treat; SEM, standard error of the mean; VA, visual acuity.
mITT population: all participants in the safety population but excluding any participant without a baseline VA score and/or any participant who did not return for at least one post-baseline visit.
1. Jackson TL, et al. Ophthalmology. 2023;130(6):588-597. 2.Data on file.

Sozinibercept Combination Therapy Demonstrates Superior Vision Gains

Vision Gain From Baseline to Week 24 (Overall Population)



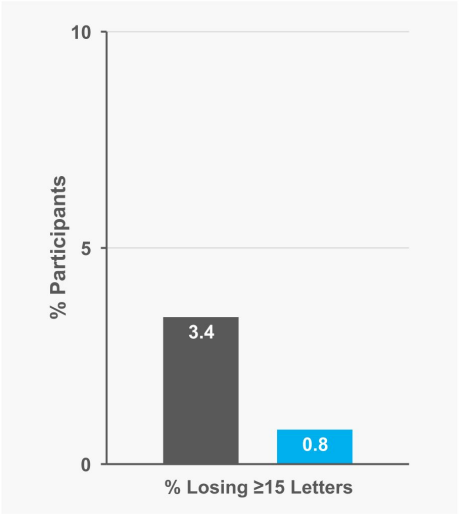
Sham + 0.5 mg ranibizumab (n=116)

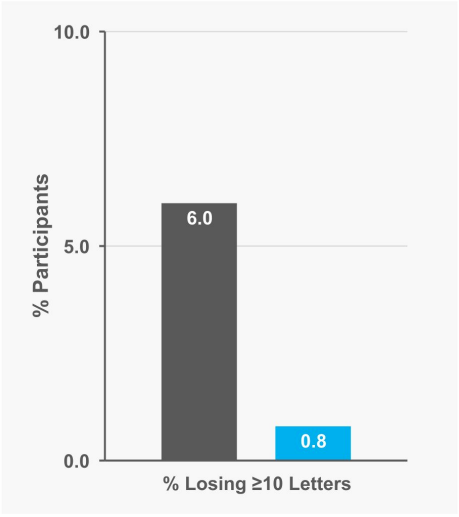
2.0 mg sozinibercept + 0.5 mg ranibizumab (n=120)

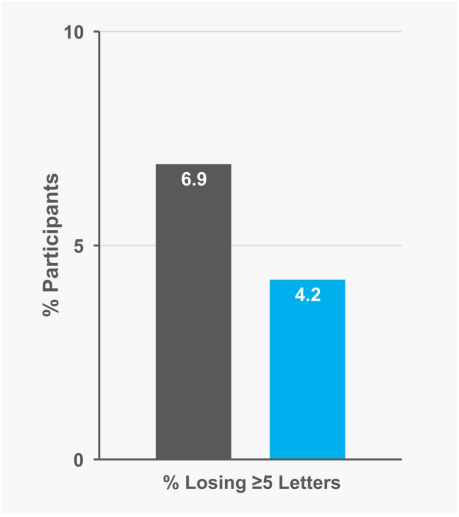
Modified intent-to-treat population; as observed.
Jackson TL, et al. Ophthalmology. 2023;130(6):588-597.

Fewer Patients Lost Vision in the Sozinibercept Combination Group

Vision Loss From Baseline to Week 24 (Overall Population)





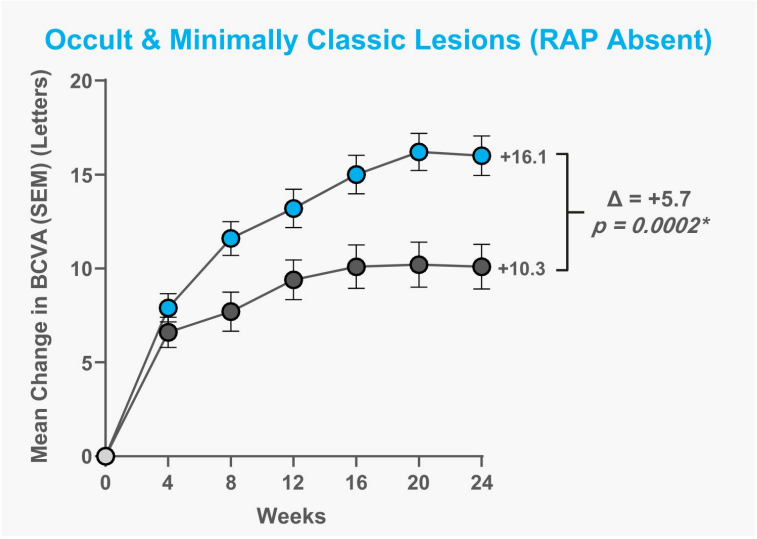


Sham + 0.5 mg ranibizumab (n=116)

2.0 mg sozinibercept + 0.5 mg ranibizumab (n=120)

Modified intent-to-treat population; as observed.
Jackson TL, et al. Ophthalmology. 2023;130(6):588-597.

Additional Improvement in Visual Acuity Outcomes With Sozinibercept Combination Therapy in Patients With Occult & Minimally Classic Lesions (RAP Absent)



Phase 2b demonstrated **superior efficacy** of a **+5.7-letter gain over standard of care** based on a **predetermined analysis**

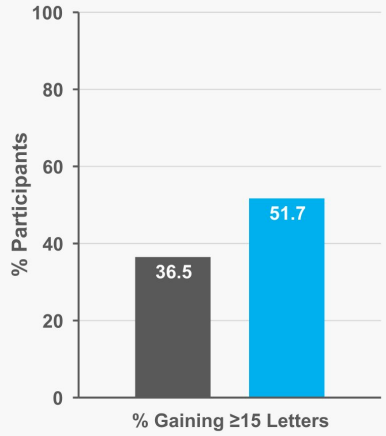
This patient population (minimally classic & occult) represents **~75% of patients with nAMD**

*Unadjusted p-value. BCVA, best corrected visual acuity; nAMD, neovascular age-related macular degeneration; RAP, retinal angiomatous proliferation; SEM, standard error of the mean.
Data on file.

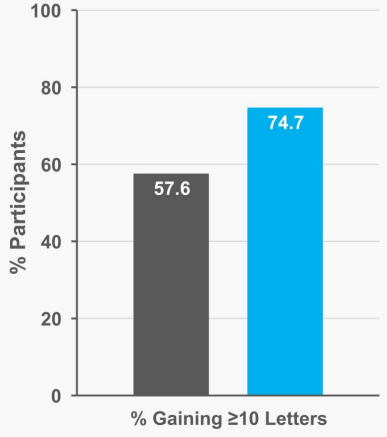
Sozinibercept Combination Therapy Demonstrates Superior Vision Gains
Vision Gain from Baseline to Week 24 (Min. Classic & Occult, RAP Absent)

Higher percentage of patients gaining ≥15, ≥10, and ≥5 ETDRS BCVA letters in sozinibercept combination group

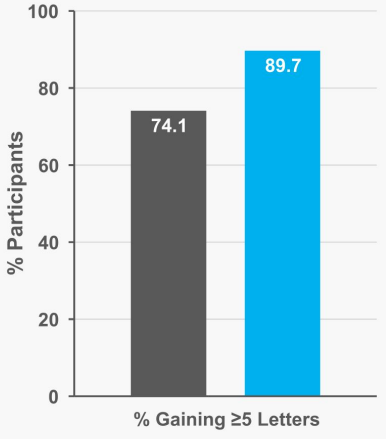
42% relative increase in % of ≥15-letter gainers compared to ranibizumab control



30% relative increase in % of ≥10-letter gainers compared to ranibizumab control



20% relative increase in % of ≥5-letter gainers compared to ranibizumab control



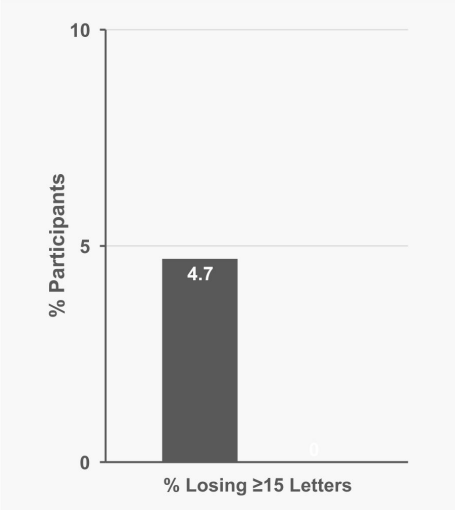
Sham + 0.5 mg ranibizumab (n=87)

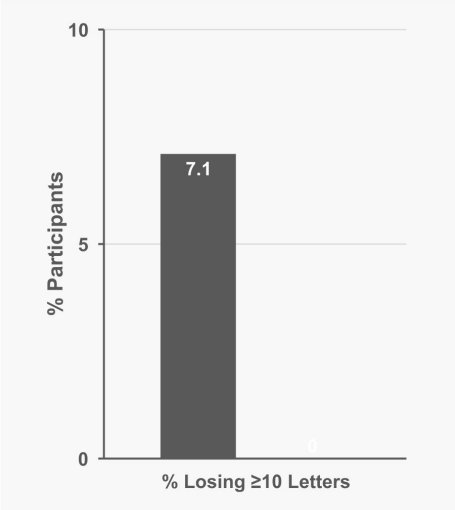
2.0 mg sozinibercept + 0.5 mg ranibizumab (n=88)

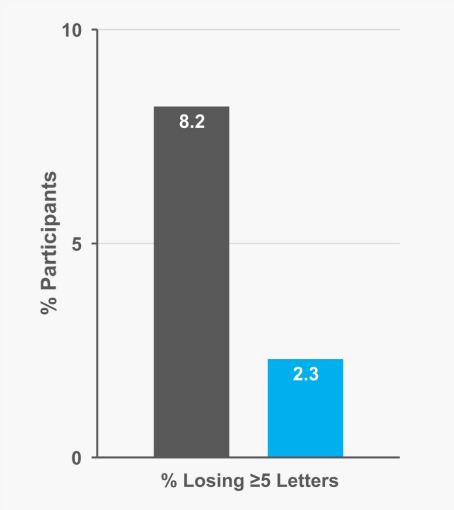
BCVA, best-corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study; RAP, retinal angiomatous proliferation.
Modified intention-to-treat (mITT) population; as observed.
Data on file.

Fewer Patients Lost Vision in the Sozinibercept Combination Group

Vision Loss from Baseline to Week 24 (Min. Classic & Occult, RAP Absent)







Sham + 0.5 mg ranibizumab (n=87)

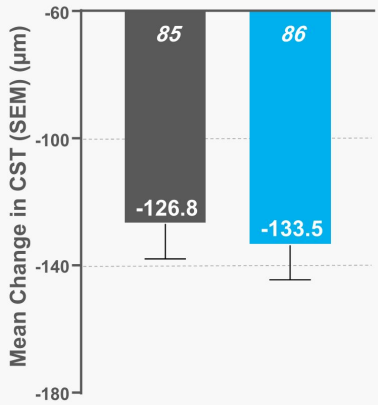
2.0 mg sozinibercept + 0.5 mg ranibizumab (n=88)

RAP, retinal angiomatous proliferation.
Modified intention-to-treat (mITT) population; as observed.
Data on file.

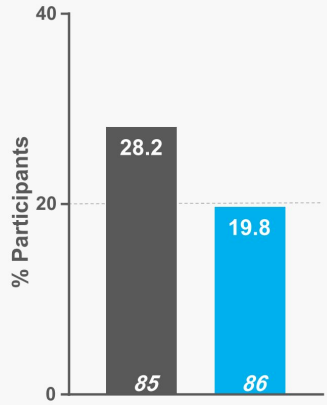
Reduced Retinal Thickness and Better Retinal Drying

With Combination Therapy in Occult & Minimally Classic (RAP Absent) Patients

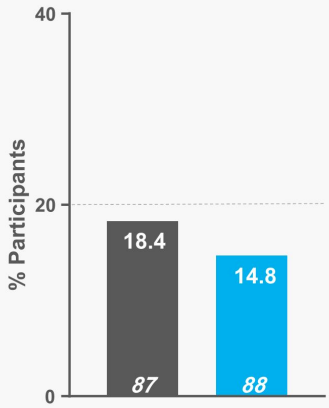
Mean Change in CST Baseline to Week 24



% of Participants With SRF at Week 24



% of Participants with IR Cysts at Week 24

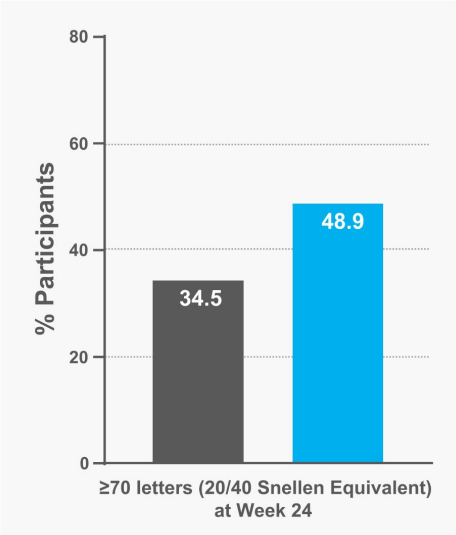


Sham + 0.5-mg ranibizumab (n=87)

2.0-mg sozinibercept + 0.5-mg ranibizumab (n=88)

Modified intention-to-treat (mITT) population; as observed; top of bar – statistic, bottom of bar – n.
CST, central subfield thickness; IR, intraretinal; RAP, retinal angiomatous proliferation; SRF, subretinal fluid.
Data on file.

Higher Percentage of Patients with 20/40 Vision or Better in Sozinibercept Combination Group (Min. Classic & Occult, RAP Absent)



Sham + 0.5-mg ranibizumab (n=87)

2.0-mg sozinibercept + 0.5-mg ranibizumab (n=88)

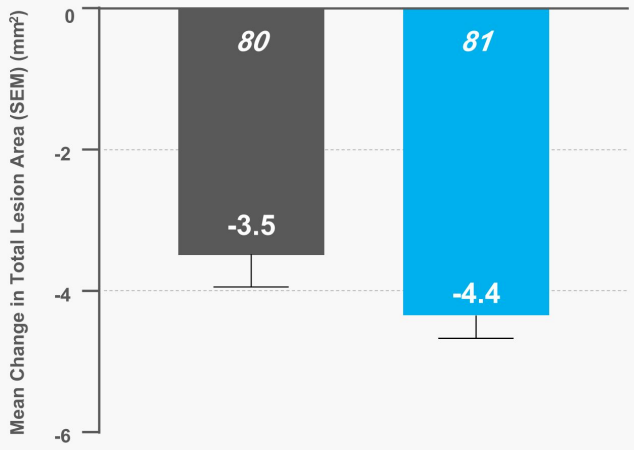
42% relative increase in % of patients with **20/40** vision at Week **24 compared** with ranibizumab control

RAP, retinal angiomatous proliferation.
Data on file.

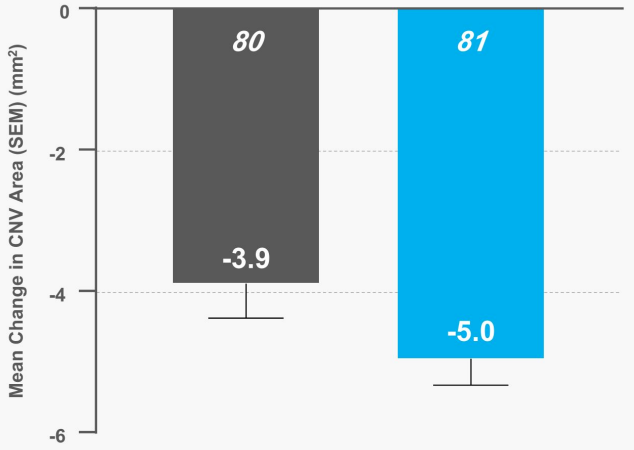
Greater CNV and Lesion Regression

With Combination Therapy in Occult & Minimally Classic (RAP Absent) Patients

Mean Change in Total Lesion Area at Week 24



Mean Change in CNV Area at Week 24



Sham + 0.5-mg ranibizumab (n=80)

2.0-mg sozinibercept + 0.5-mg ranibizumab (n=81)

Modified intention-to-treat (mITT) population; as observed; top of bar – statistic, bottom of bar – n.
CNV, choroidal neovascularization; RAP, retinal angiomatous proliferation; SEM, standard error of the mean.Data on file.

Phase 2b Safety[1,2]

Combination Therapy Well Tolerated and Comparable to Standard of Care

Participants, n (%)	Sham + 0.5-mg ranibizumab n=121	0.5-mg sozinibercept + 0.5-mg ranibizumab n=120	2.0-mg sozinibercept + 0.5-mg ranibizumab n=124
TEAEs	84 (69.4)	87 (72.5)	93 (75.0)
Ocular AEs, study eye – related to study product(s)*	17 (14.0)	17 (14.2)	19 (15.3)
Ocular AEs, study eye – severe†	1 (0.8)	2 (1.7)	1 (0.8)
SAEs	10 (8.3)	16 (13.3)	7 (5.6)
Ocular SAEs in study eye	0 (0.0)	2‡ (1.7)	0 (0.0)
Intraocular inflammation,§ study eye	2¶,# (1.7)	2‡ (1.7)	1¶ (0.8)
Participants with AEs leading to study IP discontinuation only	2 (1.7)	3 (2.5)	0 (0.0)
Participants with AEs leading to study discontinuation	1** (0.8)	0 (0.0)	0 (0.0)
Any APTC event	0 (0.0)	1†† (0.8)	0 (0.0)
Deaths	2‡‡ (1.7)	0 (0.0)	0 (0.0)

Safety population analyzed according to medication received. AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; IP, investigational product; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
*Assessed by investigator to be "possibly related," "probably related," or "definitely related" to administration of study drug(s);†Assessed by investigator to be National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or above, or, if CTCAE grade is unavailable, an AE assessed as "causing an inability to perform normal daily activities";‡SAE of endophthalmitis, with AEs of hypopyon and raised IOP and anterior chamber cell (n=1), SAE of vitritis (n=1);§AEs considered to be indicative of intraocular inflammation, defined prior to database lock as: endophthalmitis, iritis, vitritis, iridocyclitis, uveitis, hypopyon, viral iritis, or anterior chamber inflammation;¶Transient anterior chamber cell (trace 1-4 cells);#Not reported as a TEAE;**Non-Squamous cell carcinoma of the lung diagnosed shortly after baseline visit;††Non-fatal myocardial infarction; ‡‡Pneumonia (n=1), infective endocarditis (n=1). 1. Jackson TL, et al. Ophthalmology. 2023;130(6):588-597.2. Data on file.

Pooled Safety for Completed Sozinibercept Trials

Combination Therapy Well Tolerated and Comparable to Standard-of-Care Monotherapy

Participants, n (%)	Sozinibercept any dose* n=399 (n=1,842 injections)	Sozinibercept 2.0 mg n=263 (n=1,121 injections)	Sham + anti-VEGF-A control n=170 (n=854 injections)
Ocular TEAEs, study eye – related to study product(s)	41 (10.2)	22 (8.4)	20 (11.8)
Ocular TEAEs, study eye – severe	4 (1.0)	2 (0.8)	2 (1.2)
Intraocular inflammation, study eye	7[†,‡,§] (1.8)	3[†] (1.1)	3[†] (1.8)
Participants with AEs leading to treatment discontinuation	4[‡, ¶,#,**] (1.0)	1[¶] (0.4)	2[††,‡‡] (1.2)
Any APTC event	4[¶,#,§§,¶¶] (1.0)	3[#,§§,¶¶] (1.1)	2[##,***] (1.2)
Deaths	2[¶¶,†††] (0.5)	2[¶¶,†††] (0.8)	2[§§§,###] (1.2)

AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; IOP, intraocular pressure; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
*Any dose (sozinibercept 0.3 mg, 1 mg, or 2 mg); †Transient anterior chamber cell (trace 1-4 cells); ‡SAE of endophthalmitis, with AEs of hypopyon and anterior chamber cell (n=1; 0.5 mg); §SAE of vitritis (n=1; 0.5 mg); ¶Non-fatal myocardial infarction; #Cerebrovascular accident; **Enteritis; ††Abdominal pain; ‡‡Increased IOP; §§Non-fatal angina pectoris; ¶¶Fatal congestive heart failure/myocardial infarction; ##Non-fatal arterial embolism; ***Embolic stroke; †††Metastatic ovarian cancer; §§§Pneumonia; ###Infective endocarditis.
Data on file.

Phase 3 Trials:
COAST and ShORe

Near-Term Focus Is on Sozinibercept Phase 3 Execution

Pivotal Program Design Informed by Phase 2b and Optimized for Success

Completed Phase 1-2 Trials

Phase 2b (n=366)
Treatment-**naïve** nAMD
Sozinibercept: 6x monthly dosing
Comparator: ranibizumab (monthly)

Phase 1b/2a (n=153)
Prior-treated DME
Sozinibercept: 3x monthly dosing
Comparator: aflibercept (monthly)

Phase 1/2a (n=51)
Treatment-naïve/prior-treated nAMD
Sozinibercept + ranibizumab:
3x monthly dosing

Ongoing Phase 3 Trials
Topline data from both trials anticipated in mid-CY 2025

COAST	Phase 3 - nAMD (treatment naïve) n=~990	**ShORe**	Phase 3 - nAMD (treatment naïve) n=~990

Comparator: Aflibercept (Eylea®) once every 2 months after 3 monthly doses		Comparator: Ranibizumab (Lucentis®) once every month	
Standard Dosing	**Extended Dosing**	**Standard Dosing**	**Extended Dosing**
Sozinibercept once every month	Sozinibercept once every 2 months after 3 monthly doses	Sozinibercept once every month	Sozinibercept once every 2 months after 3 monthly doses

Standard of care administered according to approved dosing schedule: aflibercept 2.0 mg IVT Q8W after 3 loading doses and ranibizumab, 0.5 mg IVT Q4W after 3 loading doses. Sozinibercept dosed at 2.0 mg. Note that sham administered at visits when sozinibercept is not administered. Maintenance dosing continued through end of the safety follow-up.
CY, calendar year; DME, diabetic macular edema; IVT, intravitreal; nAMD, neovascular age-related macular degeneration; Q4W, once every 4 weeks; Q8W, once every 8 weeks.
Data on file.

Phase 3 nAMD Trials COAST and ShORe Are Well Advanced

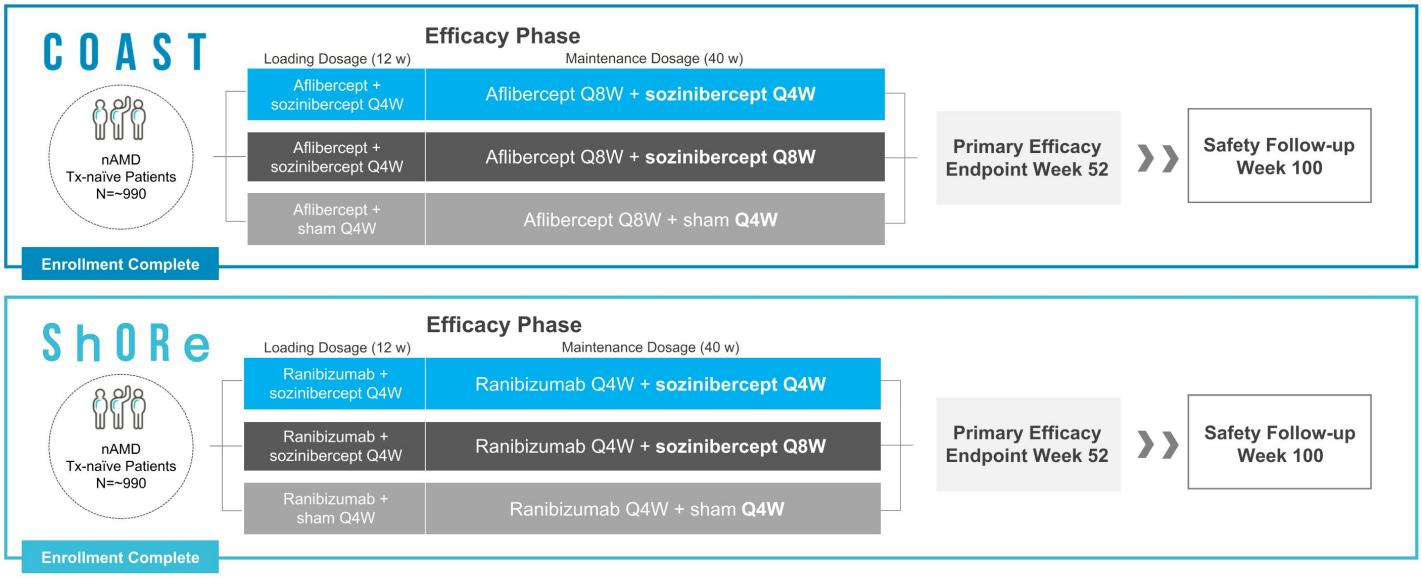
Complete Enrollment Anticipated in Q2 CY2024 | Topline Data Mid-CY2025

Design[1,2]	• Multicenter, double-masked, randomized (1:1:1), sham control • Treatment-naïve patients with nAMD
Sample Size[1,2]	• ~990 per trial • ~330 patients per arm: 2-mg sozinibercept Q4W & Q8W, or sham control
Comparators[1,2]	• 2-mg aflibercept Q8W (COAST) & 0.5-mg ranibizumab Q4W (ShORe)
Regulatory Quality[3]	• ~90% power, 5% type I error rate

CY, calendar year; nAMD, neovascular age-related macular degeneration; Q2, second quarter; Q4W, once every 4 weeks; Q8W, once every 8 weeks.

1. ClinicalTrials.gov. ShORe (NCT04757610). https://clinicaltrials.gov/study/NCT04757610. Accessed Sep 12, 2024. 2. ClinicalTrials.gov. COAST (NCT04757636). https://clinicaltrials.gov/study/NCT04757636. Accessed Sep 12, 2024. 3. Data on file

Phase 3 Trial Design Supports Potential Broad Label for Use With Any Anti-VEGF-A Therapy



Standard of care administered according to approved dosing schedule: aflibercept 2.0 mg IVT Q8W after 3 loading doses and ranibizumab, 0.5 mg IVT Q4W after 3 loading doses. Sozinibercept dosed at 2.0 mg. Note that sham administered at visits when sozinibercept is not administered. Maintenance dosing continued through end of the safety follow-up.
CY, calendar year; IVT, intravitreal; nAMD, neovascular age-related macular degeneration; Q2, second quarter; Q4W, once every 4 weeks; Q8W, once every 8 weeks; Tx, treatment; VEGF, vascular endothelial growth factor.
Data on file.

Phase 3 Inclusion and Exclusion Criteria[1,2]

Inclusion Criteria	Main Exclusion Criteria
An ETDRS BCVA score between 60 and 25 (inclusive) letters in the study eye	Any previous treatment for neovascular AMD
Active subfoveal CNV lesion or juxtafoveal CNV lesion with foveal involvement that is secondary to AMD in the study eye	Clinically significant ocular disorders (other than neovascular AMD) that may interfere with assessment of BCVA, assessment of safety, or fundus imaging
	Any current (or history of a) social, psychological, or medical condition that precludes enrollment into the study

AMD, age-related macular degeneration; BCVA, best corrected visual acuity; BLA, Biologics License Application; CNV, choroidal neovascularization; EDTRS, Early Treatment Diabetic Retinopathy Study.

1. ClinicalTrials.gov. ShORe (NCT04757610). https://clinicaltrials.gov/study/NCT04757610. Accessed Sep 12, 2024. 2. ClinicalTrials.gov. COAST (NCT04757636). https://clinicaltrials.gov/study/NCT04757636. Accessed Sep 12, 2024

Phase 3 Primary and Secondary Endpoints[1,2]

Primary Efficacy Endpoint at Week 52 to Support BLA Submission

Primary Endpoint

Mean change from baseline in BCVA at week 52

Key Secondary Endpoints (Baseline to Week 52)

Proportion of participants gaining ≥15 letters

Proportion of participants gaining ≥10 letters

Change in choroidal neovascularization area

Proportion of participants with absence of both subretinal fluid and intraretinal cysts

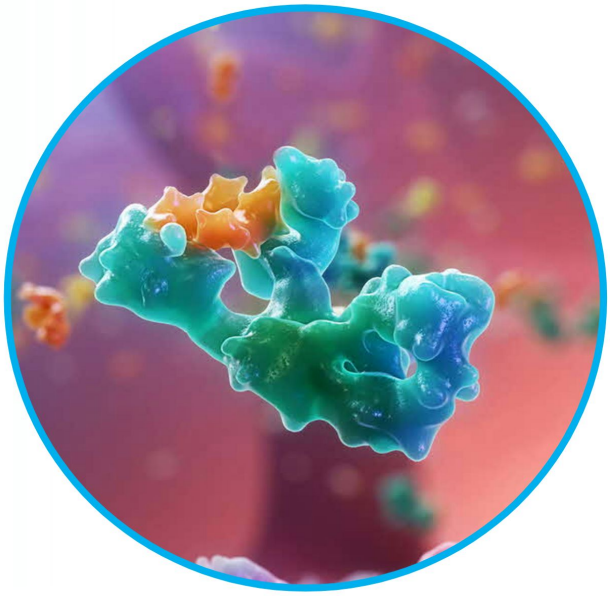
BCVA, best corrected visual acuity; BLA, Biologics License Application.

1. ClinicalTrials.gov. ShORe (NCT04757610). https://clinicaltrials.gov/study/NCT04757610. Accessed Sep 12, 2024. 2. ClinicalTrials.gov. COAST (NCT04757636). https://clinicaltrials.gov/study/NCT04757636. Accessed Sep 12, 2024.

Summary

Sozinibercept - Novel MOA, potent trap molecule that neutralizes VEGF-C and VEGF-D[1]

Potential for combination of sozinibercept and anti-VEGF standard of care to provide superior vision compared to anti-VEGF-A alone



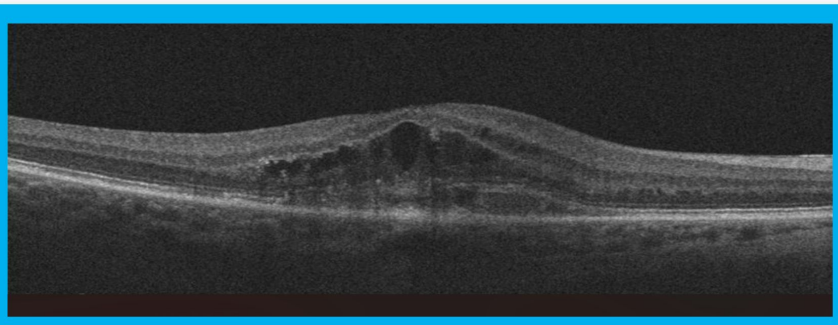
Sozinibercept
Fully Human Molecule

MOA, mechanism of action; VEGF, vascular endothelial growth factor.
1. Leitch IM, et al. Ophthalmol Ther. 2024;13:1857-1875

Panel Discussion

Speaker: Anat Loewenstein, MD, MHA

Case: Panel Discussion



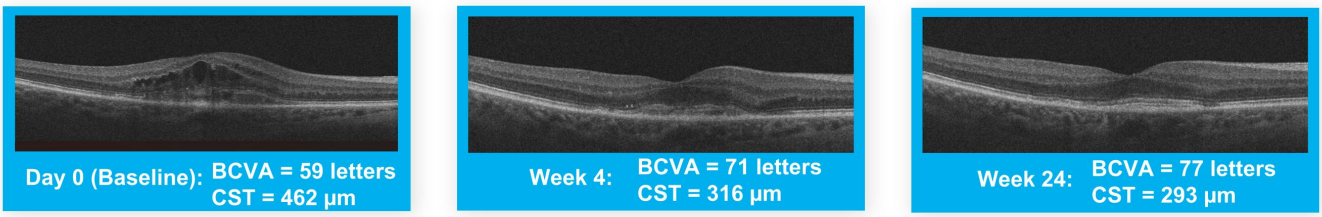
Day 0 (Baseline):

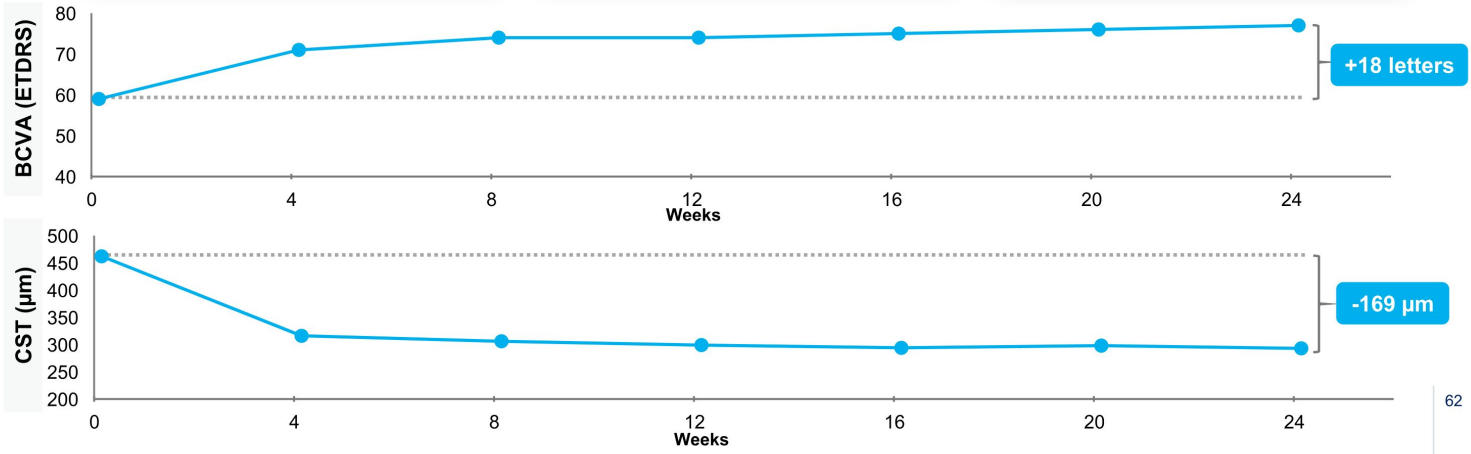
BCVA = 59 letters
CST = 462 µm

What is your drug of choice?
What is your primary treatment goal?

Ph2b Case: Treatment-Naïve nAMD Patient Receiving 2-mg Sozinibercept and Ranibizumab Combination Therapy

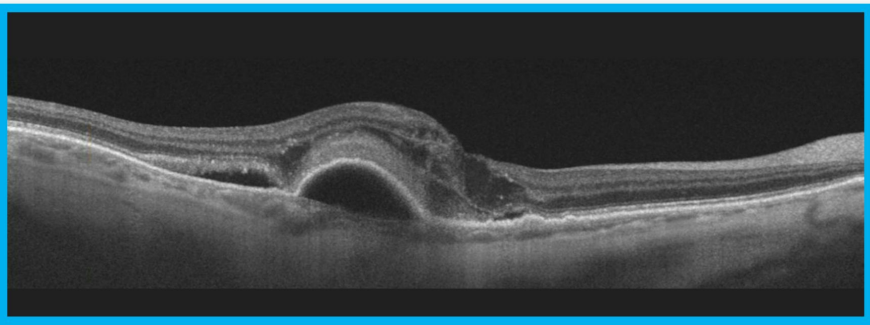
Baseline Lesion Type: Predominantly Classic





Final 6-month analysis from phase 2b trial. BCVA, best corrected visual acuity; CST, central subfield thickness; EDTRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration.

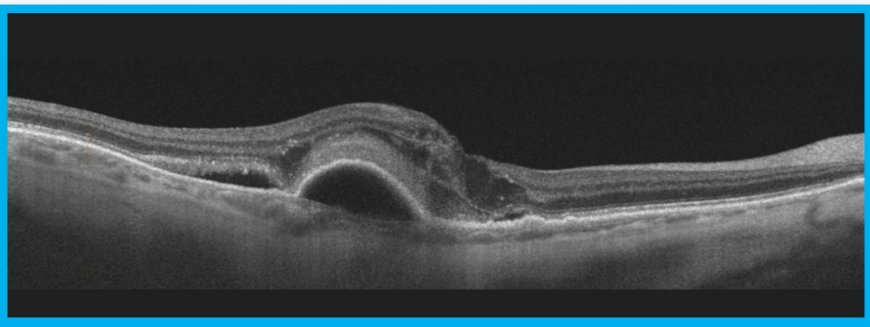
Audience Question: What Is Your Primary Treatment Goal With Anti-VEGF Therapy at 12 Months? (3-Monthly Loading Dose, Followed by Treat-and-Extend)



Day 0 (Baseline): BCVA = 55 letters (~20/80)
CST = 363 µm

- A: BCVA Improvement of 5-10 Letters
- B: BCVA Improvement of >10 Letters
- C: Achieve ≥20/40 Vision
- D: Resolution of Fluid
- E: Moderate Vision Gain and Reduction of Fluid

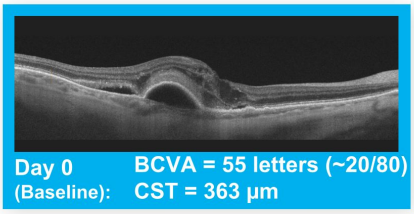
Case: Panel Discussion



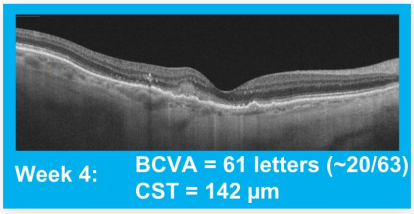
Day 0 (Baseline): BCVA = 55 letters (~20/80)
CST = 363 µm

What is your drug of choice?
What is your primary treatment goal?

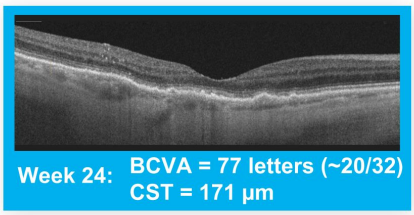
Ph2b Case: Treatment-Naïve Patient With nAMD Receiving 2-mg Sozinibercept and Ranibizumab Combination Therapy



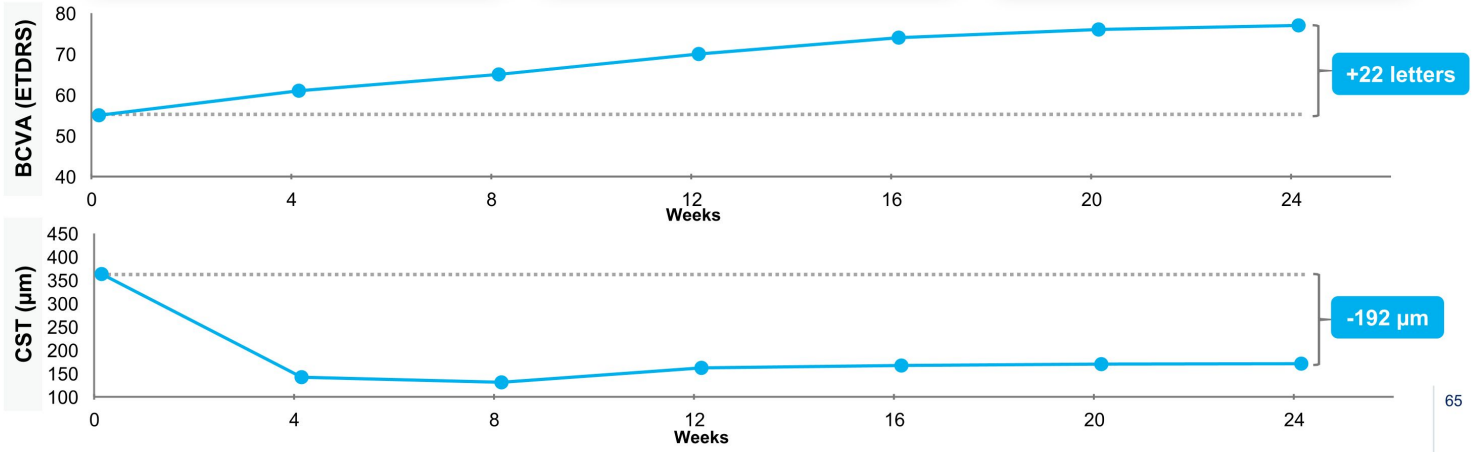
Day 0 (Baseline): BCVA = 55 letters (~20/80)
CST = 363 µm



Week 4: BCVA = 61 letters (~20/63)
CST = 142 µm



Week 24: BCVA = 77 letters (~20/32)
CST = 171 µm



Final 6-month analysis from phase 2b trial. BCVA, best corrected visual acuity; CST, central subfield thickness; EDTRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration.

Questions

Speaker: Anat Loewenstein, MD, MHA

Summary/Closing Remarks

Speaker: Anat Loewenstein, MD, MHA