Early Intervention Strategies for Dry AMD and Presbyopia

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AREDS

- First large scale study looking at nutrition and ocular health
- 3640 pts followed on average for 6.3 years
  - Results released October 2001
- Results showed that 25% risk reduction to developing advanced AMD in pts with intermediate (stage 3) AMD or worse
  - 500 mg vitamin C
  - 400 IU vitamin E
  - 15 mg vitamin A (25,000 IU beta carotene)
  - 80 mg zinc
  - 2 mg copper

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AREDS 2

- **AREDS 2: Enrollment ended June 2008 with ≈4200 patients followed for six years**
  - **Effect of lutein, zeaxanthin and omega 3 on AMD**
  - **Effect of eliminating beta carotene on AMD**
  - **Effect of reducing zinc on AMD**
  - **Effect of supplements on cataracts**
  - **Validate the AMD scale from original AREDS**
  - **Results released May 5, 2013**

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AREDS 2

- Major Conclusions:
  - The addition of lutein and zeaxanthin, DHA and EPA or both to the AREDS formulation did not further reduce the risk of progression to advanced AMD
  - Substituting L/Z (10 mg/2 mg) for beta carotene is an appropriate substitution, because of potential increased incidence of lung cancer in former smokers

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Additional findings

- Lutein and zeaxanthin did provide an additional 10% reduced risk over current supplements
  - In patients with lowest dietary intake of l/z, additional 26% reduced risk
- Decreasing zinc from 80 mg to 25 mg had no significant effect
  - No change recommended (?)
  - Deserves further study
- Competitive absorption of carotenoids

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AREDS2
Age-Related Eye Disease Study 2
The Lutein/Zeaxanthin and Omega-3 Supplementation Trial

AREDS2 Formulation

- Vitamin C (500 mg)
- Vitamin E (400 IU)
- ~~Beta-Carotene (15 mg)~~
- **Lutein (10 mg)/Zeaxanthin (2 mg)**
- Zinc (80 mg zinc oxide)
- Copper (2 mg cupric oxide)
- ~~Omega-3 fatty acids (DHA/EPA)~~

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AREDS 2 10 year study

- Released June 2022
- Followed ≅ 4K pts for an additional 10 years
- Confirmed that AREDS 2 formulation with L/Z still safer than beta-carotene
- Protective effect of AREDS2 on AMD progression continued

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GA and AREDS2

- New analysis in *Ophthalmology* looked at pts with late stage GA in AREDS/AREDS 2 study
- Showed that taking AREDS supplements slowed down lesion growth in non foveal GA by 55% over 3 years
  - Not as helpful for pts with central GA
- Consider recommending AREDS 2 supplementation for extra foveal GA pts

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PreserVision AREDS3: A Next-Gen Formula That Combines AREDS2 Nutrients With a B-Vitamin Complex

Nutrient	AREDS 2	AREDS3
Lutein	10 mg	10mg
Zeaxanthin	2 mg	2 mg
Vitamin C	500 mg	500 mg
Vitamin E	180 mg	180 mg
Zinc	80 mg	25 mg
Copper	2 mg	2 mg
Vit B1 (Thiamin)	-	**3.6 mg**
Vit B2 (Riboflavin)	-	**3.9 mg**
Vit B3 (Niacin)	-	**32 mg**
Vit B5 (Pantothenic Acid)	-	**15 mg**
Vit B6	-	**50 mg**
Vit B7 (Biotin)	-	**90 mcg**
Vit B9 (Folate)	-	**1500 mcg DFE**
Vit B12	-	**1000 mcg**

The PreserVision® AREDS3 formula will be studied in a long-term trial including patients with all stages of AMD, from early to geographic atrophy

Adds a B-vitamin complex

Per day amount reflected; take 1 soft gel with a meal 2 times per day

AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; DFE, Dietary Folate Equivalent; Vit, vitamin

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Why B Vitamins? They Support Essential Functions[1]

B1 (Thiamin)	Energy metabolism
B2 (Riboflavin)	Energy production & antioxidant reactions
B3 (Niacin)	NAD cofactor
B5 (Panothenic acid)	Fat, protein, & carbohydrate metabolism
B6	Homocysteine metabolism
B7 (Biotin)	Fatty acid & glucose metabolism
B9 (Folate)	DNA synthesis, methylation
B12	Myelin & DNA synthesis

Common dietary sources include whole grains, legumes, nuts, dairy, eggs, meat, fish, and leafy greens[1]

Approximately 10–20% of the US population has B-vitamin deficiency[1-3]

NAD, nicotinamide adenine dinucleotide; DNA, deoxyribonucleic acid

1. National Institutes of Health, Office of Dietary Supplements. Vitamin and Mineral Supplement Fact Sheets. 2024. Accessed November 10, 2025. https://ods.od.nih.gov/factsheets/list-all/. 2. Brown MJ, et al. Vitamin B6 Deficiency. Updated Aug 4, 2025. StatPearls. 2025. 3. Ellington MJ, et al. *Clin Med (Lond).* 2015;15(2):146-50.

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Multiple Studies Support the Role of B Vitamins in Reducing Incidence & Progression of AMD

› **These study points helped inform the ingredient profile for the AREDS3 formulation**

	Dietary Intake	Risk Level
B1	↑	↓ by ~45-60% for late AMD[1]
B6	↑	↓ for wet AMD[2]
B9	↑	↓ for developing GA and large drusen[2,3]
B12	↑	↓ for AMD by 42%[4]
B5, B6	↑	↓ by ~28% for advanced AMD[5]
B6, B9	↑	↓ for late AMD[2]
B1, B2, B3, B5, B6, B9, B12	↓	Observed in patients with AMD vs without AMD[6,7]

Daily Supplement	
B2 + 13 other ingredients	Stabilized atrophic AMD[8,9]
B3 + 2 other ingredients	Improved a measure of retinal function (FERG)[10]
B12 + 11 other ingredients	Functional improvement of preganglionic retinal elements[11]
B6, B9, & B12	↓ risk of AMD vs placebo by ~41%[12]

B vitamin supplementation has been found to lower levels of homocysteine, a potential contributor to AMD[13]

AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; FERG, focal electroretinogram; GA, geographic atrophy

1. Zheng Q, et al. *Ophthalmic Res.* 2019;56:150-61. 2. Agrón E, et al. *Ophthalmology.* 2021;128:625-42. 3. Merle BMJ, et al. *Am J Clin Nutr.* 2016;103:1135-44. 4. Gopinath B, et al. *Am J Clin Nutr.* 2013;98:129-35. 5. Merle BMJ, et al. *Nutrients.* 2022;14:2821. 6. Šalkovič-Kršková J, et al. *Cent Eur J Public Health.* 2023;31:140-3. 7. Liu Z, et al. *Front Nutr.* 2024;11:1504081. 8. Age-Related Macular Degeneration Study Group. *J Am Optom Assoc.* 1996;67:72-78. 9. Richer S. *J Am Optom Assoc.* 1996;67:30-49. 10. Falsini B, et al. *Ophthalmology.* 2005;110:51-60. 11. Parravano M, et al. *Adv Ther.* 2019; 36:2993-5. 12. Christen WG, et al. *Arch Intern Med.* 2009; 169:335-41.

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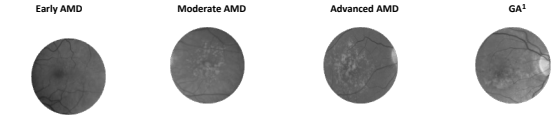
Published Studies Suggest a Wider Range of Patients May Benefit From Adding B-Vitamin Supplementation



Studies show that intake of certain **B vitamins** are associated with reduced risk of early and visually significant AMD[2,3]

AREDS 2 formula may reduce risk of progression to advanced AMD and slow GA spread toward the macula[4,5]

AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; GA, geographic atrophy

1. Rizk M, et al. *PLoS ONE* [2018] Fig 1A, CC BY 4.0. 2. Gopinath B, et al. *Am J Clin Nutr.* 2013;98(1):129–1311. 3. Christen WG, et al. *Ophthalmic Epidemiol.* 2016;23(1):32–39. 4. Age-Related Eye Disease Study Research Group. AREDS report no. 7. *Arch Ophthalmol.* 2001. 5. Keenan TDL, et al. *Ophthalmology.* 2021;132(1):44-59.

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B Vitamins May Be Supportive in Ocular Disease Beyond AMD

Condition	B Vitamins	Mechanism
Dry Eye/OSD[1,2]	B2, B6	• Promote tear secretion • Reduce inflammation via cytokine modulation
Diabetic Retinopathy[3,4]	B1, B6, B12	• Protect against oxidative stress • Neuroprotection of RGC and pericytes
Optic Neuropathy[5,6]	B12	• Neuroprotection of RGC • Reduce homocysteine levels • Myelin sheath synthesis and maintenance
Glaucoma[6]	B6, B9, B12	• Neuroprotection of RGC • Reduce homocysteine levels • Maintain ONH vascular perfusion

AMD, age-related macular degeneration; ONH, optic nerve head; OSD, ocular surface disease; RGC, retinal ganglion cells

1. Hyon JY, Han SB. *Applied Sciences*. 2022; 12(9):4567 2. Hu J, et al. *Biomedicines*. 2025;13(3):541. 3. Beltramo E, et al. *Acta Diabetol*. 2021;58(11):1433-1439. 4. Ola MS, et al. *Int J Mol Sci*. 2013;14(2):2559-72. 5. Garg P, et al. *The Pan-American Journal of Ophthalmology*. 2025;7(1):165.
6. Tribble JR, et al. *Cell Rep Med*. 2025;6(5):102127.

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Many Are At Risk of B-Vitamin Deficiency

Older adults

- Up to 20% may have subclinical B12 deficiency[1,2]
- B12 deficiency raises homocysteine levels, associated with microvascular injury in the eye[3]

Plant-based diets

- Vitamin B12 primarily obtained from animal-based sources[4]
- Vitamin B12 not naturally found in plant foods, but can be added to some (eg, cereals and nutritional yeast)[5]

Metformin-induced deficiency[6]

- Evidence suggests that long-term and high-dose metformin therapy impairs vitamin B12 (cobalamin) status

Bariatric surgery[7]

- Contributes to deficiency via lower intake and malabsorption
- Even preoperatively, 20-30% of candidates may have B-vitamin deficiency

1. Allen LH. *Am J Clin Nutr*. 2009;89(2):693S-6S. 2. O'Leary F, et al. *Nutrients*. 2010;2(3):299-316. 3. Satyanarayana A, et al. *PLoS One*. 2011;6(11):e26747. 4. Niklewicz A, et al. *Eur J Nutr*. 2023 ;62(3):1551-1559. 5. National Institutes of Health, Office of Dietary Supplements. Vitamin and Mineral Supplement Fact Sheets. 2024. Accessed November 10, 2025. https://ods.od.nih.gov/factsheets/list-VitaminsMinerals/. 6. Infante M, et al. *World J Diabetes*. 2021;12(7):916-931. 7. Al Mansoori A, et al. *Nutrients*. 2021;13(4):1383.

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What About the Safety of B Vitamins?

B vitamins are water-soluble and generally deemed safe, especially for ocular health

Clinical Adverse Events

- Five trials: No ocular adverse events with supplementation[1-6]

At-Risk Populations

- Liver disease → higher risk of niacin toxicity[7]
- Neuropathy → vulnerable to chronic high-dose B6 toxicity[8]

1. Falsini B, et al. *Ophthalmology*. 2003;110:51-60. 2. Parravano M, et al. *Adv Ther*. 2019;36:2493-505. 3. Christen WG, et al. *Arch Intern Med*. 2009;169:335-41. 4. Richer S, et al. *Optometry*. 2004;75:216-30. 5. Richer S, et al. *Optometry*. 2007; 78:213-9. 6. Azar G, et al. *J Fr Ophtalmol*. 2017;40:303-13. 7. Duffy M, et al. *Cureus*. 2024;16(9):e69518. 8. Paluszny A, et al. *Cureus*. 2023;15(11):e48792.

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Melatonin and AMD?

- Study in Jama Ophth June 2024
- Retrospective study: 230 k pts evaluated, 121K on melatonin
  - Melatonin use associated with reduced risk of AMD as well as progression
  - Pts taking melatonin As much as 58% less likely to be diagnosed with amd over 15 year study period
  - Less conversion from dry to wet amd as well
- Interesting study but flawed
  - Healthy user bias
  - Duration and diose of melatonin unclear
  - More research needed

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Pistachios?

- Tufts University Study: Journal of Nutrition, October 18, 2024
- Pistachios rich in lutein
- Eating two ounces of pistachios per day was linked to significant increase in MPOD
  - 36 healthy adults, age 40-70, with low lutein intakes
    - One group added 2 oz (two handfuls) of pistachios to daily diet, essentially doubling intake of lutein
  - MPOD levels increased at 6 and 12 weeks

*Study partially funded by American Pistachio Growers

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Metformin and AMD?

- *Ophthalmology retina* 2026
- Metformin use > 5 years was associated with a reduction in AMD risk (3.3% vs 4.9%)
  - Reduced risk of Dry, with weaker association with wet
    - Suggests may be more protective in earlier stages
  - Theory is that metformin suppresses inflammatory pathways and also has anti-angiogenic effects
- More studies needed

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Smoking and AMD

- Smoking has been shown in multiple studies to be the #1modifiable risk factor for getting AMD as well as its progression
- **One study showed 90% of pts with AMD were not advised to quit smoking**
- **<50 of smokers knew that smoking could may contribute to blindness**

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Smoking and AMD

- Nurses health study
  - 2.5 fold increase in AMD in current smokers
  - 2.0 fold increase for past smokers
  - Former smokers did not show decreased risk until 15 years after cessation
  - 30% of all AMD related top smoking

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Smoking and AMD

- Blue Mountain Eye Study: Australia 1992-1994
  - Current smokers had a 4-fold increase in late AMD compared with never-smokers
  - Former smokers had a 3 fold increase in late AMD, esp GA
  - 20% of all cases of blindness related to smoking

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Smoking and AMD

- New research: *Retina* 2020
  - Current smokers have up to a 7-fold greater risk for nAMD vs non-smokers
    - more aggressive , larger CNVM and worse baseline va in smokers
    - Current smokers were 6.2 years younger than nonsmokers needing treatment
  - Pts who smoked while undergoing anti-vegf treatment experienced inferior 12 and 24 month visual outcomes

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Diet and AMD

- 2018 Study:
  - 4446 European pts >55
  - Seen every 5 years for 21 years on average
    - Adherence to Mediterranean Diet reduced risk of advanced AMD by 41%
    - Support role of diet rich in fruits, vegetables, legumes and Fish in prevention of AMD

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Diet and AMD

- 2016
  - Meta-analysis looking at 4202 cases in 128,988 individuals
  - Fish consumption reduced risk of both early and late AMD
  - Both for less than as well as more than 10 year follow up
  - Dark meat fish, esp. tuna fish, intake was associated with reduced risk of AMD
  - Linear association between dose of fish consumption and risk of AMD demonstrated

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Diet and AMD

- 2019
  - Meta-analysis looking at 26 articles consisting of 211,676 subjects with 7154 cases of AMD from 8 studies
    - 18% reduced risk for total AMD with increased fish intake, both early and late
    - 20% increased risk for total AMD with increased alcohol consumption
    - Increased risk for meat consumption for early AMD, but not late
    - No association with fruits, vegetables, nuts, grain or dairy

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Diet and AMD

- 2018: Rotterdam Eye Study
  - 4200 pts>55 years followed for 9.1 +/- 5.8 years
  - 754 developed AMD
  - Determined a diet of 200 grams per day of vegetable, fruit two times per day, and fish two times per week is associated with a significantly reduced risk of AMD
    - Only 3.7% of patients adhered to this

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Diet and AMD

- 2006
- 6734 pts followed for 13 years
  - Red meat more than 10x a week had a additional 47% risk of developing AMD vs those who ate red meat 5 times or less per week, especially early AMD
  - Chicken (white meat) 3.5 times a week had 60% chance less risk of AMD vs. those who ate 1.5 times a week, especially late AMD

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Exercise and AMD

- 2017 Meta-Analysis, 9 studies, age range 30-97
- Physical activity associated with lower odds of early and late AMD in white population
  - More pronounced with Late AMD
- Suggested that even a small amount of physical activity-as little as 3 hrs per week- may be beneficial

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Exercise and AMD

- Beaver Dam study
  - 4000 men and women 43-86 years old
  - Those who exercised 3 or more times a week had 70% lower risk for late amd (active lifestyle)
  - 30% lower rates of WET AMD in pts who walked 12 or more blocks 3 times a week

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Obesity and AMD

- Progression of Age-Related Macular Degeneration Study.
  - 2003, Seddon et al
  - Increased risk for advanced AMD with BMI>25
    - Even more increased if BMI >30
  - Higher waist –hip ration also increased risk for progression
  - 25% reduction for vigorous activity 3x /week vs none
  - Other studies have been less conclusive

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UV and AMD

- 2016 Study
  - Current sunlight exposure showed no association with early or late AMD
  - Past sunlight exposure (>8 hrs /day) was associated with early AMD
  - Outside working was associated with late AMD
  - No association with iris color and early or late AMD
  - "Sunlight exposure during working life is and important risk factor for AMD, whereas sunlight exposure after retirement has less influence on the disease"

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UV and AMD

- Beaver Dam Study
  - Pts 43-86. 2764 followed for 10 years
  - People exposed to summer sun for >5 hrs while in teens and 30s were at higher risk of developing AMD at 10 years vs those who had less than 2 hrs
  - Those that were exposed >5hrs but reported wearing hats and wearing sunglasses were at decreased risk vs those that did not
  - People who reported 10 or more severe sunburns during youth vs 1 or no burn were at higher risk

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How do I use this information?

- Don't smoke
- Exercise regularly
- Keep other medical conditions under control
- Maintain a healthy weight
- Eat a diet high in fruits, vegetables, and fish
- Limit consumption of red meat and foods high in fat
- **Protect eyes from sunlight with UV protection and sunglasses**
- **Take supplements as prescribed by your doctor**
- Follow-up as recommended

Gerson J, et al. *Rev Optom*. 2017;suppl:1-11 (www.revoptometry.com/CMSDocuments/2017/10/maculogist.pdf). Accessed 7/14/2021.

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Valeda® Light Delivery System

Valeda Overview

- Valeda treatment delivery very similar to many ophthalmology office diagnostic and treatment devices
- Implementation support available from LumiThera Customer Success Team
- Treatment is simple to learn and easy to train for operators
- No pupil dilation required
- Nine (9) flexible treatment sessions delivered over 3–4 weeks
- 2-3 treatment cycles per annum

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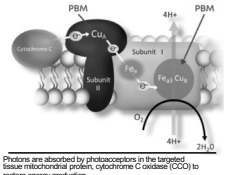
Photobiomodulation (PBM) Approach

PBM uses low-level light to stimulate cells to restore energy production and improve cellular health



Photons are absorbed by photoacceptors in the targeted tissue mitochondrial protein, cytochrome C oxidase (CCO) to restore energy production

Sustained cellular changes also occur through activation of transcription factors

Valeda Wavelengths (nm)	Cellular Targets	Secondary Effects
590	Stimulates CCO activity, increases nitric oxide (NO) synthesis, inhibits VEGF expression	Vasodilation, Improves local O_2 and nutrient delivery, VEGF reduction
660	Promotes O_2 binding to CCO active Cu_B/Fe_{a3} site	Upregulates Electron Transport Pathway, Increases energy (ATP), Reduces Inflammation and cell death
850	Drives electron transfer at Cu_A site of CCO	Upregulates Electron Transport Pathway, Increases energy (ATP), Reduces Inflammation and cell death

Valeda wavelengths were selected based on their cellular targets and importance in AMD

Wong-Riley MTT, et al. J Biol Chem. 2005; 280: 4761-71; Ball KA, et al. J Photochem Photobiol B Biol, 2012; 102: 182-91.

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FDA Authorizes Breakthrough Valeda Therapeutic for Dry AMD to Improve Vision (November 04, 2024)

Valeda Light Delivery System

- Five successful clinical studies
- US LIGHTSITE III pivotal trial data met BCVA primary endpoint
- Data from two-year LIGHTSITE III trial used to support Valeda FDA submission
- First FDA authorized therapy for Dry AMD Patients to improve vision
- CE marked: Available in Europe and other countries
- Non–invasive, safe therapy for patients

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First FDA treatment for Dry AMD Patients to Improve Vision

Indications for Use:

The Valeda Light Delivery System is intended to provide improved visual acuity in patients with best corrected visual acuity (BCVA) of 20/32 through 20/70 and who have dry age-related macular degeneration (AMD) characterized by:

- The presence of at least 3 medium drusen (> 63 µm and 125 µm in diameter), or large drusen (> 125 µm in diameter), or non-central geographic atrophy, AND
- The absence of neovascular maculopathy or center-involving geographic atrophy

After about two years, the Valeda Light Delivery System treatment provides improved mean visual acuity of approximately one line of visual acuity (ETDRS) compared to those not receiving the treatment.

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LIGHTSITE III: Safety Summary

- Similar frequencies of adverse events (AE) (Sham, 25.5%; PBM, 25.8%) and ocular-specific AEs (Sham, 20.0%; PBM, 22.6%) observed between treatment groups
- Three subjects had ocular-specific AEs considered related to the procedure: punctate keratitis (Sham; n = 2; 3.6%), visual perseveration (after image) (Sham; n = 1; 1.8%), and application site warmth (PBM; n = 1; 1.1%). No ocular-specific AEs led to study discontinuation.
- Seven (7.5%) ocular-specific serious adverse events (SAE) of nAMD were reported in the PBM group and three (5.5%) ocular-specific SAEs (2 nAMD, 1 cystoid macular edema) were reported in the Sham group. No SAEs were considered associated to the treatment by the primary investigator.
- Severity of AEs reported were mostly mild/moderate in both treatment groups
- No signs of phototoxicity
- No adverse effect on color vision or perimetry

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LIGHTSITE III: Study Summary

LIGHTSITE III study results show significant effect on clinical and anatomical outcomes that support vision improvement and disease modifying effects

- LIGHTSITE III met the primary efficacy endpoint with a statistically significant improvement in BCVA in the PBM versus the Sham group
- Eyes with worse BCVA at baseline showed larger magnitude gains in BCVA
- Increased rate of > 5, 10, and 15 letter BCVA gains following PBM compared to BCVA loss in the Sham group
- Cox proportional analyses showed a significant reduction in the hazard ratios for BCVA vision loss and incident GA in PBM vs Sham treatment groups
- Reduced occurrence of incident GA and other exploratory markers of disease progression
- Reduced macular drusen volume
- Improved QoL in VFQ-25 Composite score and select subscales
- A favorable safety profile was observed with no signs of phototoxicity and no deterioration in other visual outcomes, including contrast sensitivity, low luminance BCVA, Radner reading, perimetry, or color vision observed

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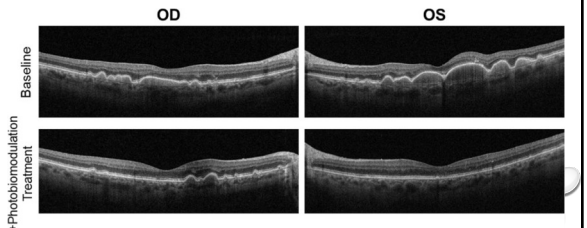
- 73 yo male
- 8 mos of PBm
  - OD: bcva stabilized at 20/25
  - OS: bcva 20/30 to 20/20



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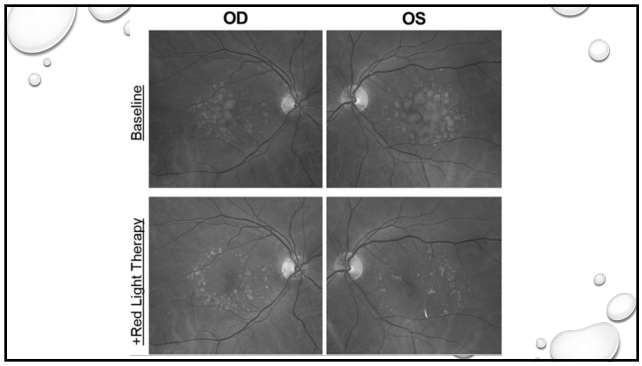

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GA treatments

Syvore (Pegcetacoplan)

- Apellis
- Blocks c 3
- FDA approved Feb 2023
- Delivered intravitreally every 25-50 days

Izervay (ACP)

- Astellas
- Blocks c5
- Fda approved august 2023
- Delivered intravitreally every month

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Why do genetic testing?

- Increased surveillance for those at higher risk
  - Sooner/more frequent appointments
  - More diligent home monitoring
- More diligence with modifiable risk factors
- Consider earlier vitamin supplementation
- Potential treatments in the future

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Is AMD in our DNA?

- **AMD is a genetic disease with known markers accounting for at least 70% of the population attributable risk**
- **Other 30% is environmental/lifestyle**
- **Risk factors**
  - **Non-modifiable: age, race, gender**
  - **Modifiable: Smoking, increased BMI, poor diet/nutrition, UV exposure**

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AMD Genetic Testing: Arctic DX

Macula Risk NXG

Looks at 15 SNPs as well as smoking, BMI, age and AMD status to determine AMD patients who may progress to advanced AMD and vision loss in

- 2 years
- 5 years
- 10 years

Cheek Swab

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AMD Risk Testing for a Full Spectrum of Patients

AMDiGuard DNA Progression Assessment

For people ≥55yo with or without AMD findings

For people <55yo WITH AMD findings

- Assesses a patient's risk of progression to advanced AMD within 2, 5,10, 20 and 30 years
- Delaying progression to advanced AMD with secondary prevention including AREDS vitamins, increased surveillance (home monitoring)

AMDiGuard DNA Risk Assessment

For people <55yo without AMD findings

- Assesses a patient's lifetime risk of developing advanced AMD (GA or CNV) *allowing preventive lifestyle changes at younger age*
- Delaying onset of disease with primary prevention including lifestyle modifications, supplementation (i.e. nutrition) and nutritional intervention

Visible GENOMICS

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Visible Genomics AMD Gene Panel

- Based on the latest in AMD Genetics research
- Clinically Proven and Clinically Actionable to be the most impactful variations on AMD progression
- Combines both genetic + non-genetic markers

23andMe SNPs

Gene	SNP No.	Allele Variants	AMD Risk	Chromosome	Pathway
ARMS2/HTRA1 (HtrA Serine Peptidase 1)	Rs10490924 (A69S)	GG	Lower Risk (Reference)	10q26	Immune/ inflammatory
		GT	Moderate Risk		
		TT	Higher Risk		
CFH (Complement Factor H)	Rs1061170 (Y402H)	TT	Highly Protective	1q31	Complement
		CT	Moderately Protective		
		CC	Higher Risk (Reference)		
	Rs121913059 (R1210C)	CC	Lower Risk (Reference)		Complement
		CT	Moderate Risk		
		TT	Higher Risk		
	Rs1410996 (IVS14)	AA	Highly Protective		Complement
		GA	Moderately Protective		
		GG	Higher Risk (Reference)		
C3 (Complement Component 3)	Rs2230199 (R102G)	GG	Lower Risk (Reference)	19p13	Complement
		GC	Moderate Risk		
		CC	Higher Risk		

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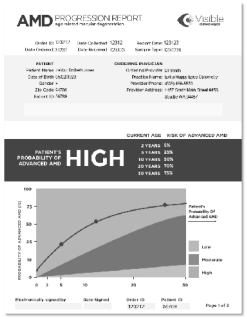

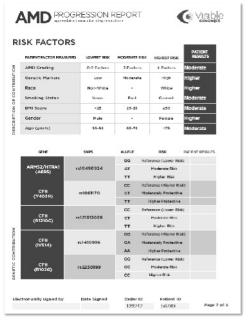

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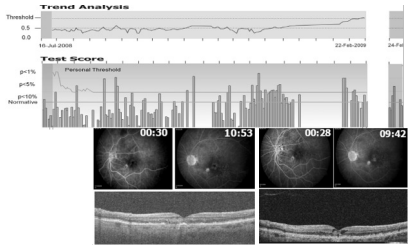
Recent study: seddon et al. *ophthalmology*

- Looked at "high Genetic risk" patients based on Genetic risk score
- Unhealthy behaviors increased incidence of Advanced AMD by 3-5 fold
- 56-60% of incidence related to modifiable factors
  - Smoking
  - High BMI
  - High caloric intake
  - Low intake of foods risk in L/Z/Omegas 3s
- Strengthens the importance of lifestyle management in those populations at high risk, such as pts with high genetic risk

Seddon JM, Reynolds R, Rosner B. Validation of a genetic risk score for macular degeneration: replication and extension in an independent sample. Ophthalmology. 2015

49

Foresee Home



50

At-risk Patients May Convert to Wet AMD at Any Point Between Follow-up Visits

Visit **1** — Visit **2**

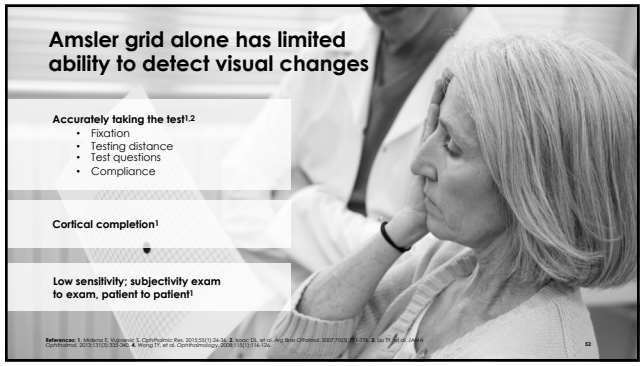
Converts after office visit	Converts between office visits	Converts before office visit
More likely to lose vision		Less likely to lose vision

Reference: Bausch R, et al. *Retina*. 2012;32(7):1260-1264.

51

51

Amsler grid alone has limited ability to detect visual changes



Accurately taking the test[1,2]
- Fixation
- Testing distance
- Test questions
- Compliance

Cortical completion[1]

Low sensitivity; subjectivity exam to exam, patient to patient[1]

References: 1. Midena E, Vujosevic S. Ophthalmic Res. 2015;55(1):24-36. 2. Isozo DI, et al. Arq Bras Oftalmol. 2007;70(5):771-774. 3. Liu TY, et al. JAMA Ophthalmol. 2013;131(3):335-340. 4. Wang TY, et al. Ophthalmology. 2008;115(1):14-134.

52

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AREDS2-HOME Study

ForeseeHome plus standard care arm	Intent to Treat (ITT) population results	Standard care arm
763 participants	1520 participants	757 participants
51 CNV events	Mean follow up 1.4 yr ± 0.6 years Mean VA at entry 20/25	31 CNV events
• Routine monitoring • Patient symptoms • ForeseeHome		• Routine monitoring • Patient symptoms

***Primary outcome:** Change in BCVA from baseline to CNV detection*

Reference: AREDS2-HOME Study Research Group. *Ophthalmology*. 2014;121(2):535-544.

53

53

ForeseeHome Arm

Intent to Treat (ITT)

Per Protocol 1 (PP1) — Per Protocol 2 (PP2)

at least 1 test throughout the study

≥ 2x per week (8x per month)

Reference: AREDS2-HOME Study Research Group. *Ophthalmology*. 2014;121(2):535-544.

54

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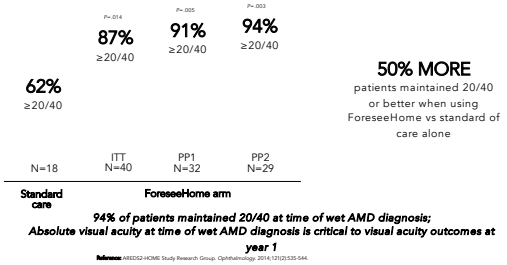
More patients who used ForeseeHome maintained ≥20/40 VA



94% of patients maintained 20/40 at time of wet AMD diagnosis; Absolute visual acuity at time of wet AMD diagnosis is critical to visual acuity outcomes at year 1

Reference: AREDS2-HOME Study Research Group. Ophthalmology. 2014;121(2):535-544.

55

55

Home OCT

- Monitoring of intra- and subretinal fluid based on daily patient self-imaging
  - Easy-to-use, patient-operated device
  - Takes less than one minute per eye
  - AI algorithm analyzes images on cloud
  - Remote diagnostic clinic, provider of monitoring program, reports changes meeting physician-selected fluid volume thresholds to referring physician
  - 24/7 physician access to all data
- Great way for retina MDs to know when next injection truly needed

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Home OCT

- SCANLY AI Powered home OCT approved 5/16/24
- Two us trials over 500 pts
  - Safe and efficacious way to visualize intra and sub-retinal edema
  - 5,426 scans performed, 97% successful
  - Adherence of 5.9 scans/week
  - Self-imaging took 44 seconds on average

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OKKO Health

Home-monitoring to ensure that first anti-VEGF treatment and re-treatment happens on time.

Clinical intro deck | 2026

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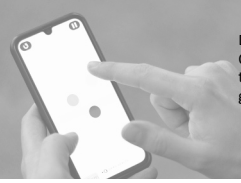
OKKO Health is a UK-based software medical device company enabling between-appointment home-monitoring of vision in macular disease



Developed by vision scientists and Ophthalmologists, OKKO brings clinical-grade testing to smartphones, using simple puzzle games

OKKO's partners and research collaborators

Oxford University Hospitals NHS Foundation Trust · Nottingham University Hospitals NHS Trust · Topcon Healthcare · Moorfields Eye Hospital NHS Foundation Trust · Macular Society Beating Macular Disease · Bayer

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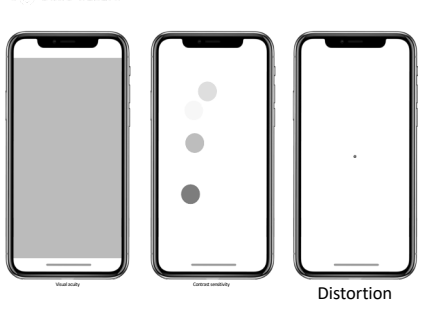
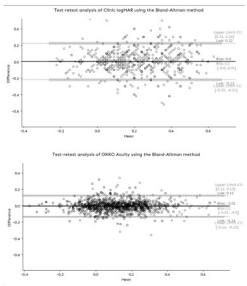


60



Test-retest repeatability of OKKO acuity scores compares favourably to ETDRS scoring, showing increased precision in a real-world cohort.

Comparative Bland Altman analysis of OKKO and ETDRS acuity scores show a mean difference of 3.5 letters, indicating clinical agreement between the two measures.

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OKKO is now available for AMD in the US

- ☑ FDA cleared (510k exemption route)
- ☑ HIPAA compliant
- ☑ Dual certified: ISO 13485 and ISO 27001
- ☑ US patent granted
- ☑ US trademark granted
- ☑ Investment from Topcon Healthcare (2025)

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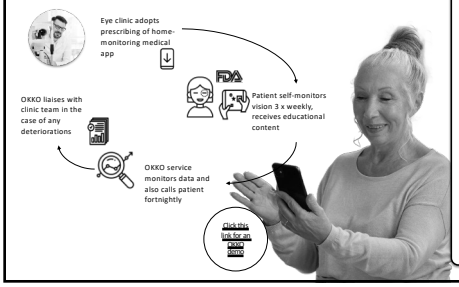
Tech-enabled service business



OKKO's average user age is 77, using our software on their own smartphone, unassisted.

Hardware-free, low cost and globally scalable.

Modular tech setup is ready for multi-geography and multi-language deployment.

Where a patient's vision scores or symptoms changes, OKKO will be in touch to triage and assist the fast-track back to clinic.

63

Benefits to EYE clinics:

1. Designed to become a safety-net between appointments: particularly suitable to support long-acting treatments
1. Better patient confidence and doctor-patient communication
1. Home-monitoring opens up new clinical revenue stream for clinics

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Presbyopia Impacts Quality of Life

Functionality	Aesthetic
Falls / Hip Fractures, Head Injuries	Psychological
Mental Health	Productivity/ Occupation

Loss of Near Vision ranks as having the most significant impact on quality of life compared to other age-related ailments

Burke Healthcare Research. April 2020, n = 1,000 presbyopes

65

Traditional Presbyopia Solutions

OPTICAL

- Glasses
  - Negative impact on self confidence
  - Inconvenient
  - Fogging

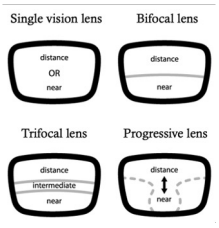

Image credit: www.bettervisionguide.com

66

Traditional Presbyopia Solutions

OPTICAL

- Contact Lenses
  - Inconvenient
  - CL-related dry eye
  - Compliance issues

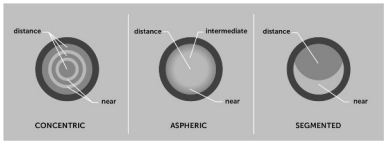

Image credit: skyvisioncenters.com

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Presbyopia Pharmaceutical Treatments:

- Presbyopia drops reduce pupil size temporarily
- Assess pupil size before prescribing presbyopia drops
- Monitor side effects, particularly in low-light conditions
- Counsel patients on getting the most out of their presbyopia drops

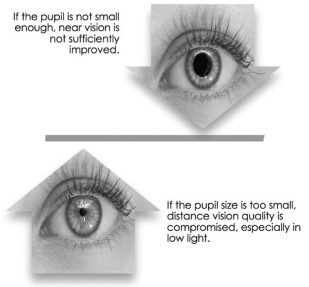

Image Credit: Presbyopia Management: Exploring Options for Today's Patient. (2021) Cataract & Refractive Surgery Today.

68

Key Considerations for Topical Presbyopia Treatments

Maximize duration of effect
What percentage of patients will be using this habitually vs situationally?

Minimize onset time
How do you gauge what onset time is important to your patients?

Limit reduction of distance and night vision
How do you discuss night vision expectations with your patients?

Minimize adverse events
How do you counsel patients about side effects?

Minimize impact on ocular surface health
How important is ocular surface health when considering these topical presbyopia treatments?

Maximize drop administration comfort to increase compliance
How does drop administration comfort affect patient compliance?

Patient selection pearls for presbyopia drops. Review of Ophthalmology. https://www.reviewofophthalmology.com/article/patient-selection-pearls-for-presbyopia-drops#:~:text=Patient%20hesitation%20most%20often%20centers,Epitropoulos%20says. Updated January 13, 2026. Accessed March 5, 2026.

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Presbyopia Pharmaceutical Treatments

Agent	Composition	MOA	Status
Aceclidine			
Vizz (Lenz)	1.75% aceclidine	Pupil modulation	US FDA-Approved July 2025
Carbachol			
Brimochol (Visus/Tenpoint)	2.75% carbachol + 0.1% brimonidine	Combination of pupil modulation and ciliary body contraction	FDA-Approved January 2026
Phentolamine			
MR-141 (Opus Genetics/Viatris)	0.75% phentolamine	Combination of pupil modulation and ciliary body contraction	Phase 3 trial completed; not yet submitted to FDA
Pilocarpine			
Qlosi (Orasis)	0.4% pilocarpine	Pupil modulation	US FDA-approved 2023; commercially available April 2025
Vuity (AbbVie)	1.25% pilocarpine	Pupil modulation	US FDA-approved 2021

Table adapted from: Dell S.J. (2 Pharmacologic treatments for presbyopia. (2024). Cataract & Refractive Surgery Today. Retrieved from https://crstoday.com/articles/july-2024/pharmacologic-treatments-for-presbyopia. Ophthalmology Times. https://www.ophthalmologytimes.com/view/the-emerging-era-of-presbyopia-correcting-eye-drops-what-s-next . Updated August 20, 2025. Accessed August 29, 2025. FDA Approves Yuvezzi, First Dual-Agent Eye Drop for Presbyopia. https://eyewire.news/news/fda-approves-yuvezzi-first-dual-agent-eye-drop-for-presbyopia?c4src=article:infinite-scroll. Updated January 26, 2026. Accessed March 5, 2026.

70

Pilocarpine 1.25%
Dosing and Treatment-Related Adverse Events

- Dosing: once or twice daily, with second dose after 3 to 6 hours
- Preservative: Benzalkonium chloride (BAK)
- GEMINI 1; GEMINI 2; VIRGO

Treatment-related AEs	GEMINI 1		GEMINI 2		VIRGO	
	Pilocarpine 1.25% group - 163, n (%)	Vehicle group - 159, n (%)	Pilocarpine 1.25% group - 212, n (%)	Vehicle group - 215, n (%)	Pilocarpine 1.25% group - 114, n (%)	Vehicle group - 116, n (%)
Headache	23 (14.11)	15 (9.43)	33 (15.57)	11 (5.12)	10 (8.77)	4 (3.45)
Blurring of vision	4 (2.5)	1 (0.6)	13 (6.13)	1 (0.47)		
Conjunctival hyperemia	4 (2.5)	4 (2.5)	15 (7.08)	11 (5.12)		
Eye irritation	4 (2.5)	1 (0.6)			114 (6.14)	0
Eye pain	4 (2.5)	1 (0.6)	12 (5.66)	3 (1.40)		

Singh M, et al. A Systematic Review and Meta-Analysis on the Efficacy and Safety of Topical Pilocarpine 1.25% in Presbyopia Treatment. J Curr Ophthalmol. 2025;36(2):111-121.

71

Pilocarpine 1.25%
Efficacy

- 1.25% of pilocarpine was used either once (in the GEMINI 1 and GEMINI 2 trial) or twice daily (VIRGO trial).
- A significantly higher proportion of patients reported improvement of DCIVA and gain of ≥ 3 lines in binocular DCNVA in the pilocarpine group than the vehicle group ($P < .01$).

Why wasn't this treatment more widely adopted?

Singh M, et al. A Systematic Review and Meta-Analysis on the Efficacy and Safety of Topical Pilocarpine 1.25% in Presbyopia Treatment. J Curr Ophthalmol. 2025;36(2):111-121.

72

Pilocarpine 0.4%
Dosing and Treatment-related Adverse Events

- Dosing: once or twice daily, with second dose after 3 to 6 hours
- Preservative Free
- NEAR-1 and NEAR-2 trials (N = 613)

Treatment-Related AEs	CSF-1 n = 308; n (%)	Vehicle n = 305; n (%)
Non-Ocular		
Headache	21 (6.8%)	2 (0.7%)
Eye/facial pain	6 (1.9%)	1 (0.3%)
Nausea	4 (1.3%)	
Ocular		
Instillation site pain	18 (5.8%)	1 (0.3%)
Vision blurred	11 (3.6%)	2 (0.7%)
Conjunctival hyperemia	5 (1.6%)	1 (0.3%)
Instillation site pruritus	3 (1.0%)	1 (0.3%)
Visual impairment	3 (1.0%)	

Holland E, et al. Efficacy and Safety of CSF-1 (0.4% Pilocarpine Hydrochloride) in Presbyopia: Pooled Results of the NEAR Phase 3 Randomized, Clinical Trials. Clin Ther. 2024;46(2):104-113.

73

Pilocarpine 0.4%
Efficacy

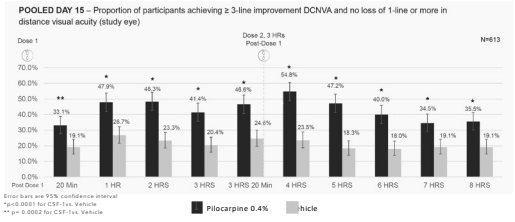
Pooled Results of NEAR 3 Phase 3 Trial

- The 2-dose regimen was evaluated twice-daily drop during a 2-week period
- 40% achieved the FDA endpoint of a 3-line gain on day 8 at 1 hour post dose compared with 19% of the vehicle group, with similar results out to 4 hours
- Among those who could not achieve 20/40 near at baseline, approximately 80% had functional (20/40) near vision on day 15, with efficacy out to 8 hours.
- Lowest effective concentration of any miotic
- Effective at a minimum effective dose, possibly because of its near-neutral pH among other factors, which increases bioavailability
- Includes sodium hyaluronate and hydroxypropyl methylcellulose (lubricants for comfort)

Holland E, et al. Efficacy and Safety of CSF-1 (0.4% Pilocarpine Hydrochloride) in Presbyopia: Pooled Results of the NEAR Phase 3 Randomized, Clinical Trials. Clin Ther. 2024;46(2):104-113.

74

Pilocarpine 0.4%
Efficacy



Holland E, et al. Efficacy and Safety of CSF-1 (0.4% Pilocarpine Hydrochloride) in Presbyopia: Pooled Results of the NEAR Phase 3 Randomized, Clinical Trials. Clin Ther. 2024;46(2):104-113.

75

Aceclidine 1.75%
Dosing and Treatment-related Adverse Events

- Dosing: once daily
- Preservative Free
- CLARITY-1 and CLARITY-2 Trials (N = 466); CLARITY 3 (N = 217)

Treatment-Related AEs	Aceclidine 1.75%*
Instillation site irritation	20%
Dim vision	16%
Conjunctival hyperemia	8%
Ocular hyperemia	7%
Headache	13%

*Vehicle comparisons have not been shared

Optometry Times. https://www.optometrytimes.com/view/fda-approved-lenz-therapeutics-vizz-for-the-treatment-of-presbyopia. Updated July 31, 2025. Accessed August 29, 2025.

76

Aceclidine 1.75%
Efficacy

- The company reported that 71%, 71%, and 40% of participants in the phase 3 trials achieved the FDA endpoint at 0.5 hours, 3, and 10 hours on day 1, with higher percentages achieving 2-line gains
- The drug was studied out to 6 months

LENZ Therapeutics announces positive topline data from phase 3 CLARITY presbyopia trials. News release. LENZ Therapeutics. April 3, 2024. Accessed August 29, 2025. https://ir.lenz-tx.com/news-events/press-releases/detail/1116/lenz-therapeutics-announces-positive-topline-data-from-phase-3-clarity-presbyopia-trials

77

Carbachol 2.75% and Brimonidine Tartrate 0.1% (fixed combination)

- Dosing: once daily
- Preservative Free
- BRIO-I and BRIO-II Trials: two pivotal phase 3 trials (N = 811)

BRIO-I: No treatment-related serious adverse events were reported.

BRIO-II: No treatment-related serious adverse events were reported after up to 12 months of continuous dosing.

Clinical Trial Vanguard. Brio-II Phase 3 Study Shows Positive Topline Data for Brimochol PF in Presbyopia Treatment. http://www.businesswire.com/news/home/20250109824922/en/Tenpoint-Therapeutics-Announces-Positive-Topline-Data-from-Phase-3-Pivotal-Study-BRIO-II-of-BRIMOCHOL%E2%84%A2-PF-for-the-Treatment-of-Presbyopia. Updated January 10, 2025. Accessed August 29, 2025.
Eyewire News. https://eyewire.news/news/visus-therapeutics-presents-topline-clinical-data-from-phase-3-pivotal-brio-i-trial-of-brimochol-pf-for-the-treatment-of-presbyopia-at-eyecelerator-at-ascrs-2023?c4src=article:infinite-scroll. Updated May 6, 2024. Accessed August 29, 2025.
https://eyewire.news/news/visus-therapeutics-presents-topline-clinical-data-from-phase-3-pivotal-brio-i-trial-of-brimochol-pf-for-the-treatment-of-presbyopia-at-eyecelerator-at-ascrs-2023?c4src=article:infinite-scroll
Optometry Times. https://www.optometrytimes.com/view/tenpoint-therapeutics-announces-positive-topline-results-from-phase-3-pivotal-trial-brio-ii-assessing-brimochol-pf-for-the-treatment-of-presbyopia. Updated January 9, 2025. Accessed August 29, 2025.

78

Carbachol 2.75% and Brimonidine Tartrate 0.1% Efficacy

- ~85% of subjects had functional near vision of 20/40 or better at 1 hour, with ~ 50% still 20/40 or better at 10 hours
- The combination demonstrated an increase in peak effect and duration over carbachol alone
- The pupil constricts within 30 minutes and then gradually returns to normal throughout the day, with no tachyphylaxis in pupil response or near vision over the 12-month study
- *This is believed to be the only company to have measured reading speed using a validated scale in its clinical trials, reporting a 39% improvement, reflecting functional gains rather than simply improvements in visual acuity*

McCabe C...Ophthalmology Times. https://www.ophthalmologytimes.com/view/the-emerging-era-of-presbyopia-correcting-eye-drops-what-s-next- The emerging era of presbyopia-correcting eye drops: What's next? Updated August 20, 2025. Accessed August 29, 2025.

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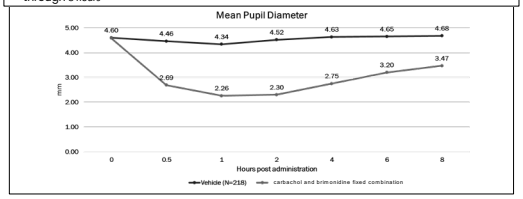
Efficacy: Carbachol and Brimonidine

- Differences between carbachol and brimonidine fixed combination and vehicle highly significant (P<0.001) at all timepoints
- Within optimum pupil range for mesopic and low light conditions at most timepoints through 8 hours



1. Xu R, Thibos L, Bradley A. Effect of target luminance on optimum pupil diameter for presbyopic eyes. *Optom Vis Sci.* 2016; 93(11):1409-1419.

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Topical Presbyopia Treatments
Things to Consider for Each Patient

1. Maximize duration of effect
2. Minimize onset time
3. Limit reduction of distance and night vision
4. Minimize adverse events
5. Minimize impact on ocular surface health
6. Maximize drop administration comfort to increase compliance

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