

Emerging Treatments in Geographic Atrophy

Reason for Hope?

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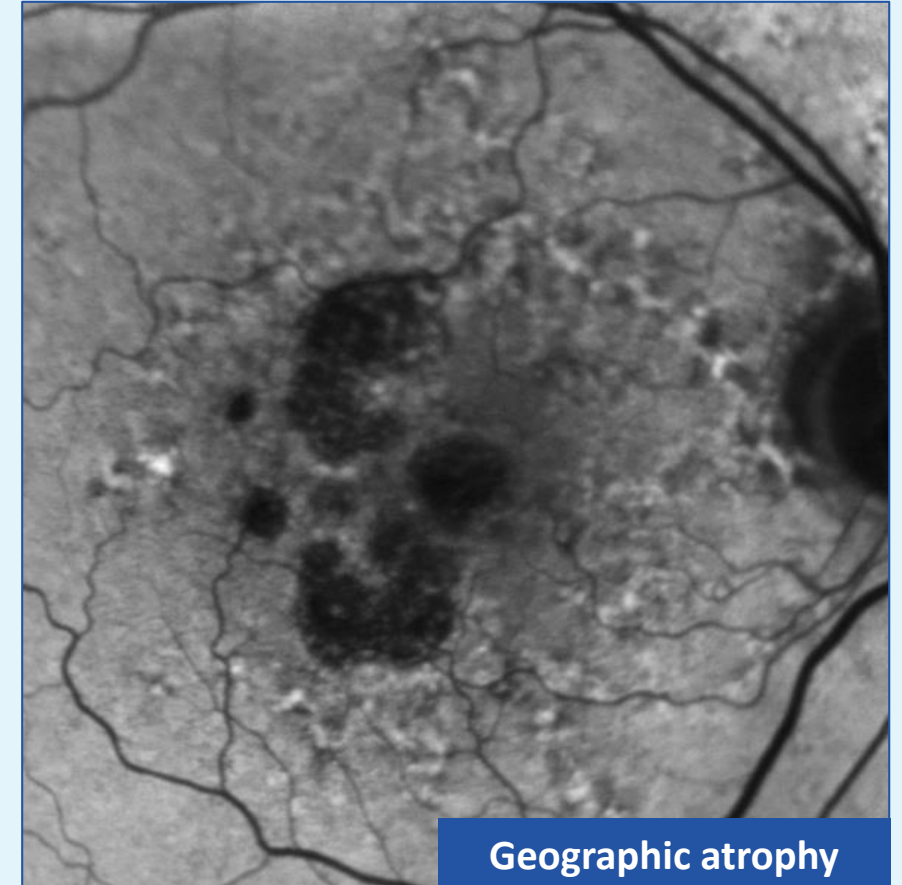
Learning Objectives

- 01 Recognize the burden of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) and its negative impact on quality of life
- 02 Evaluate the latest efficacy and safety data from clinical trials of complement system inhibitors
- 03 Review current and emerging approaches for monitoring and treating GA



GA Overview

- GA is an advanced form of vision-threatening AMD^[a]
- Up to 20% of people with AMD develop GA^[a,b]
 - Usually associated with the dry subtype
- GA is characterized by distinct atrophic lesions in the outer retina, caused by the loss of photoreceptors, retinal pigment epithelium, and choriocapillaris^[a]
- GA leads to progressive and irreversible vision loss and significantly reduced QoL
- Until recently, there were no FDA-approved treatments for GA
 - In early 2023, the complement C3 inhibitor pegcetacoplan received FDA approval^[c]
- A variety of other treatments are being actively explored



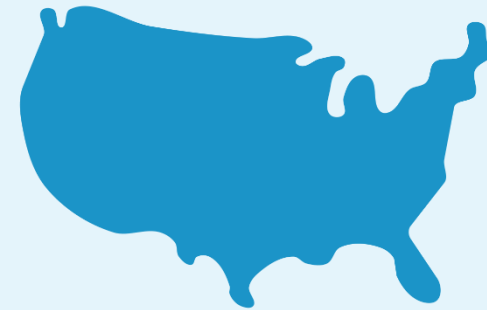
QoL, quality of life.

a. Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390; b. Friedman DS, et al. *Arch Ophthalmol*. 2004;122:564-572; c. Charters L. [Ophthalmology Times](#). Published February 17, 2023. Accessed June 14, 2023.

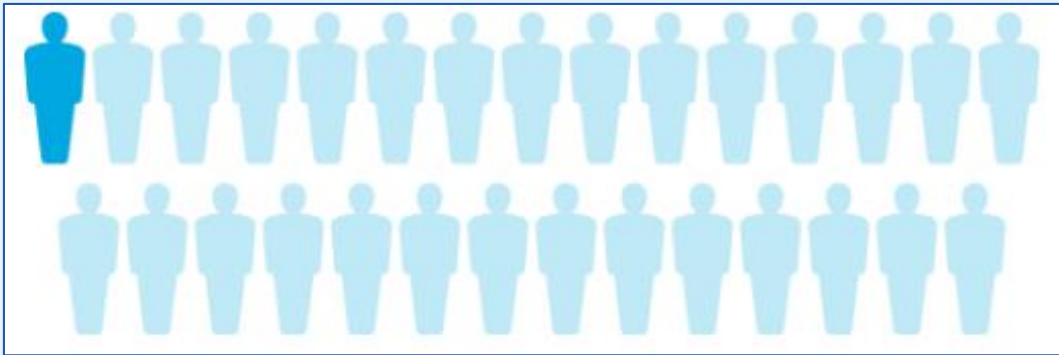
GA Prevalence



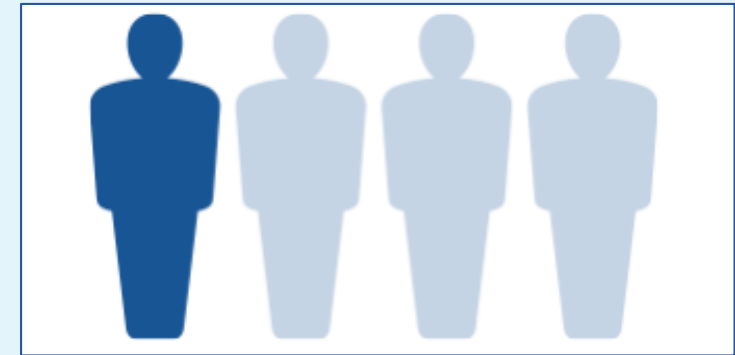
> 5 million people worldwide have GA^[a]



Includes ~1 million people in the United States^[a]



~1 in 29 people aged > 75 years have GA^[b-d]



Reaches 1 in 4 in people aged > 90 years^[e]

GA Risk Factors

Many modifiable and nonmodifiable risk factors have been observed for GA^[a]

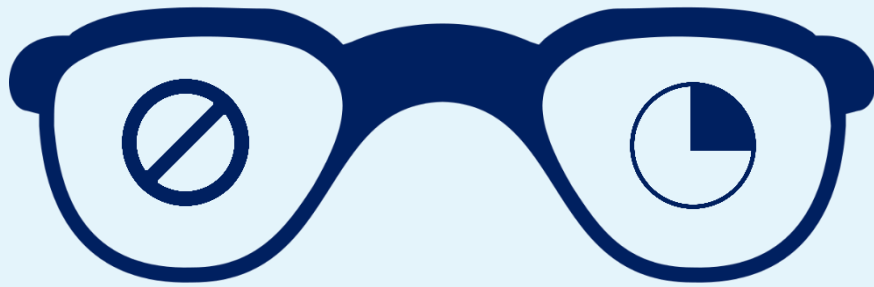
Modifiable^[b-d]

- **Smoking**
- Poor diet
- Obesity
- Cardiovascular disease, including diabetes and elevated total/HDL cholesterol levels

Nonmodifiable^[b,d,e]

- **Older age**
- **Family history**
- European ancestry
- Light-colored eyes
- Presence of a genetic variant (eg, at the *CFH*, *ARMS2/HTRA1* locus)

Impact on Vision



42% of patients' eyes with GA are **legally blind** (20/200 or worse with best correction)^[a]



29% of patients' eyes with GA had **≥ 6 lines of vision loss** on an eye chart by 4 years^[b]

Impact on Patient QoL

GA leads to considerable burden among those affected

Associated with loss of visual acuity and independence when performing tasks

68%

GA patients who report the impact on their independence and QoL say it is worse than they expected

70%

GA patients who rely on a caregiver for support

85%↑

Most GA patients feel aspects of their everyday life are negatively impacted (eg, ability to read, drive, travel)

30%↑

Many people with GA experience emotional hardships, anxiety, feelings of powerlessness, and frustration

Monitoring GA

GOAL: Detecting AMD in its early stages is crucial because individuals could potentially benefit from medications currently being studied for GA^[a]

FAF^[b]

- Current gold standard for monitoring progressive GA enlargement
- Allows more reproducible measure of atrophic areas, better lesion boundary discrimination, and provides information on expected progression rate

OCT^[c]

- Also provides important information
- Enables clear visualization of the retinal layers
- Can help in early identification of intraretinal fluid and provide information of expected progression rate

FAF, fundus autofluorescence; OCT, optical coherence tomography.

a. Loewenstein A, et al. Graefes Arch Clin Exp Ophthalmol. 2023;2611525-1531; b. Sacconi R, et al. Ophthalmol Ther. 2017;6:69-77;

c. Nielsen MK, et al. [AAO EyeWiki](#). Published December 19, 2021. Accessed June 14, 2023.

Monitoring Patients – A Discussion



What is your strategy for monitoring patients with GA?

Targeting the Complement Pathway

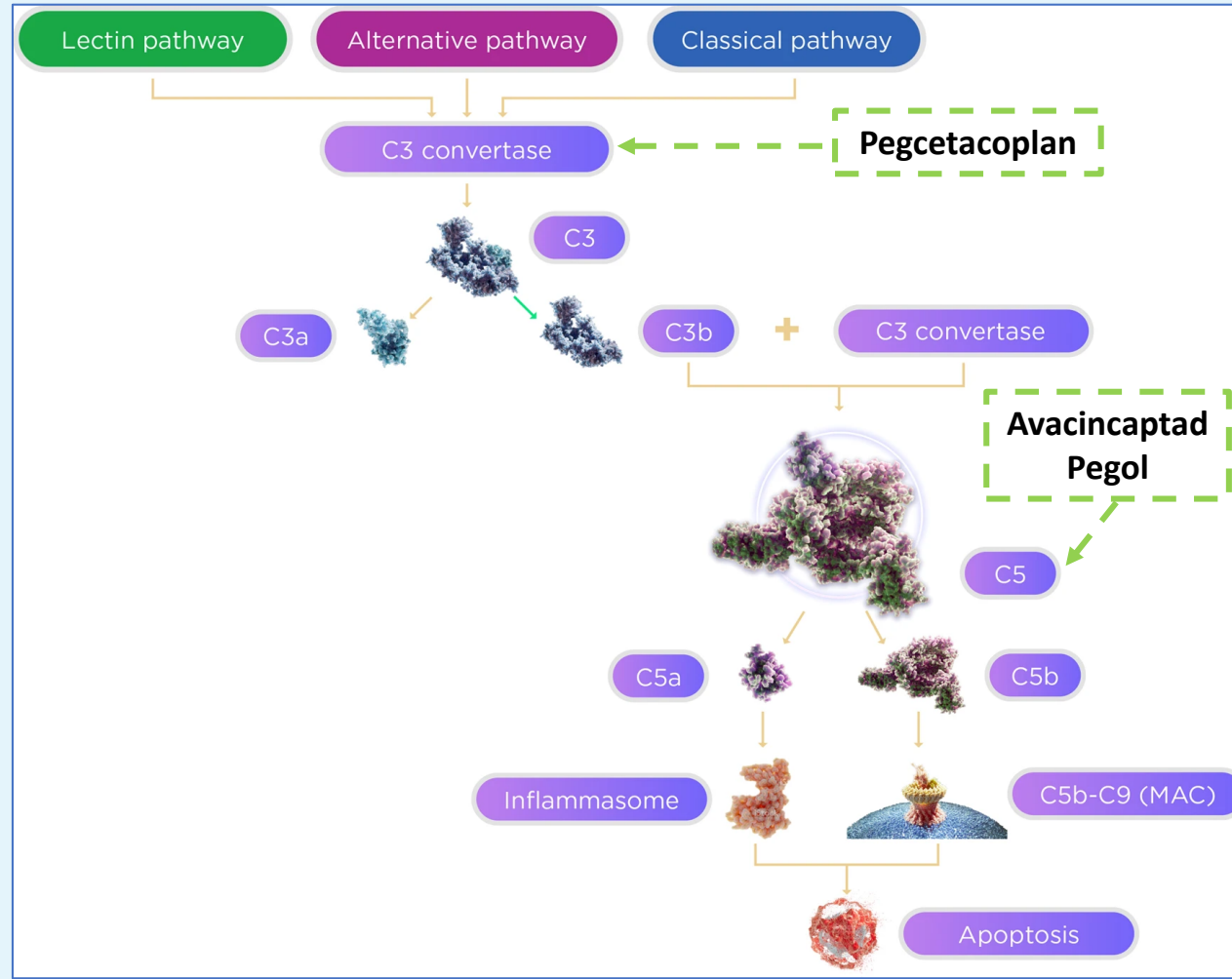
Complement-Targeting Treatments for GA

- Complement system is part of innate immune system and has been implicated in development of GA^[a]
- C3 and C5 complement inhibitors have demonstrated efficacy and safety in phase 3 clinical trials^[a]
- **Pegcetacoplan** and **avacincaptad pegol** belong to class of drugs that target complement system
 - **Pegcetacoplan** acts as a complement C3 inhibitor^[b]
 - Currently only FDA-approved treatment for GA
 - **Avacincaptad pegol** functions as a complement C5 inhibitor^[c]
 - In phase 3 clinical trials, with available data showing promising efficacy and safety



Many other treatments are being actively explored, signaling hope in treating patients with GA

Complement Cascade and Targeted Inhibition

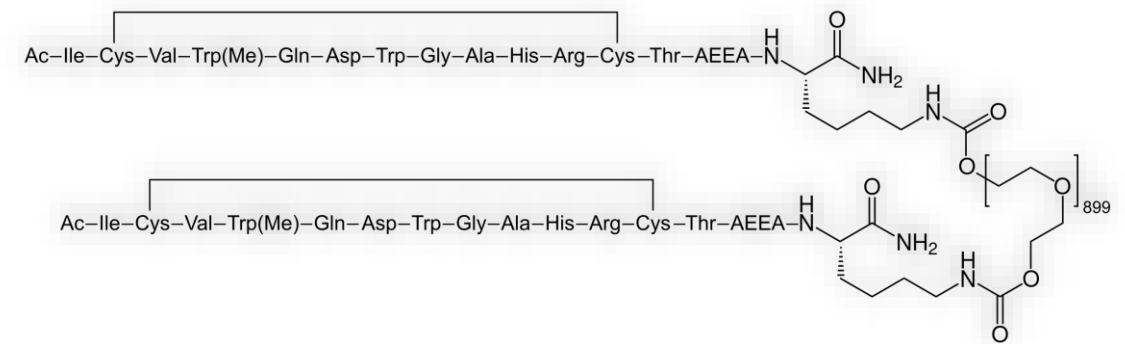


Pegcetacoplan Overview

First and only FDA-approved treatment for GA secondary to AMD^[a,b]

- 15 mg administered by intravitreal injection to each affected eye once every 25 to 60 days^[b]
 - Contraindicated in patients with ocular or periocular infections or active intraocular inflammation
- Efficacy and safety established in the randomized phase 3 OAKS and DERBY clinical trials^[c]
 - FDA approval based on the 24-month efficacy data

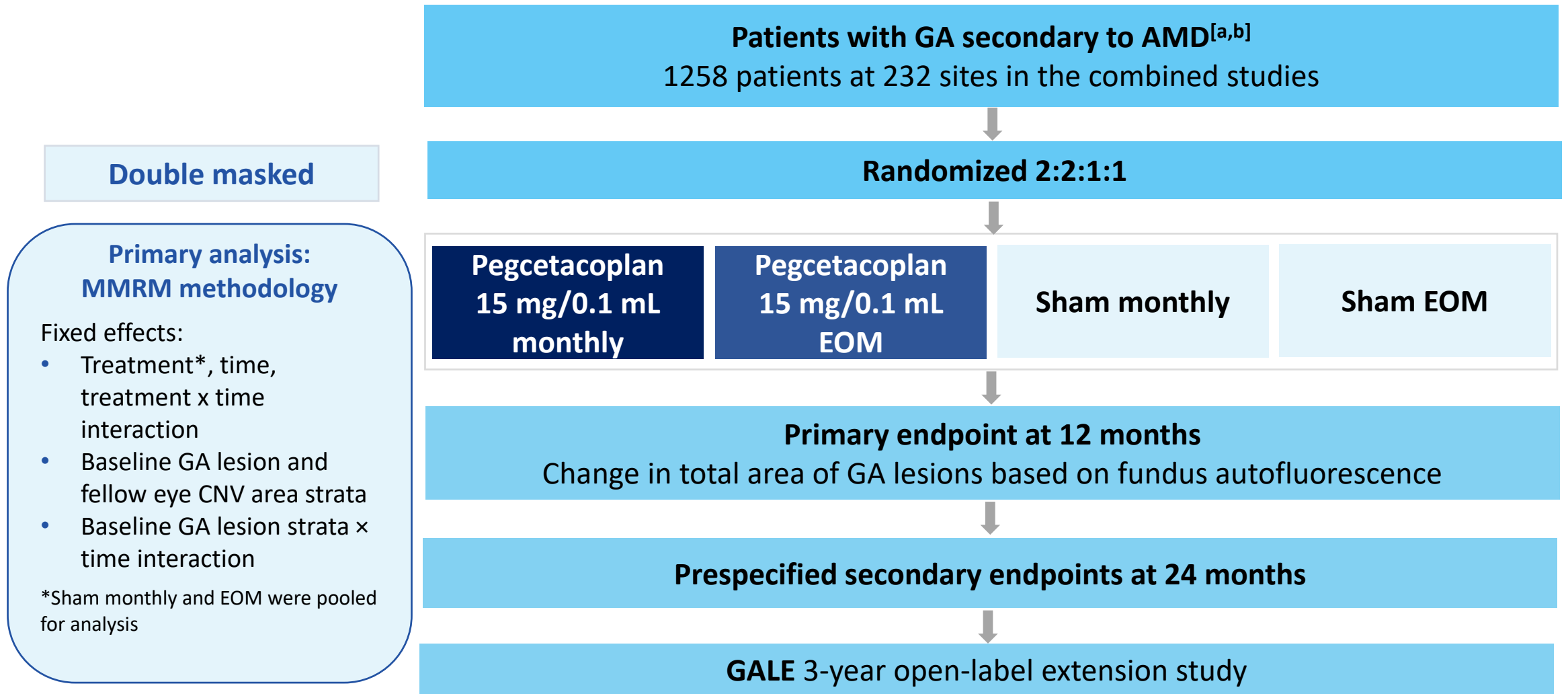
Structure of Pegcetacoplan



a. Enoch J, et al. Eye (Lond). 2023(May 11):1-9; b. Pegcetacoplan injection [[prescribing information](#)]. Approved 2021. Revised February 2023;

c. Charters L. [Ophthalmology Times](#). Published February 17, 2023. Accessed June 14, 2023.

OAKS and DERBY: Design



OAKS and DERBY: Inclusion/Exclusion Criteria



Key Inclusion Criteria

- Age \geq 60 years
- BCVA \geq 24 letters ETDRS (20/320 Snellen equivalent)
- GA lesion requirements:
 - Total size: \geq 2.5 and \leq 17.5 mm²
 - GA lesions with or without subfoveal involvement allowed
 - If multifocal, \geq 1 focal lesion must be \geq 1.25 mm² (0.5 DA)
 - Perilesional hyperautofluorescence present



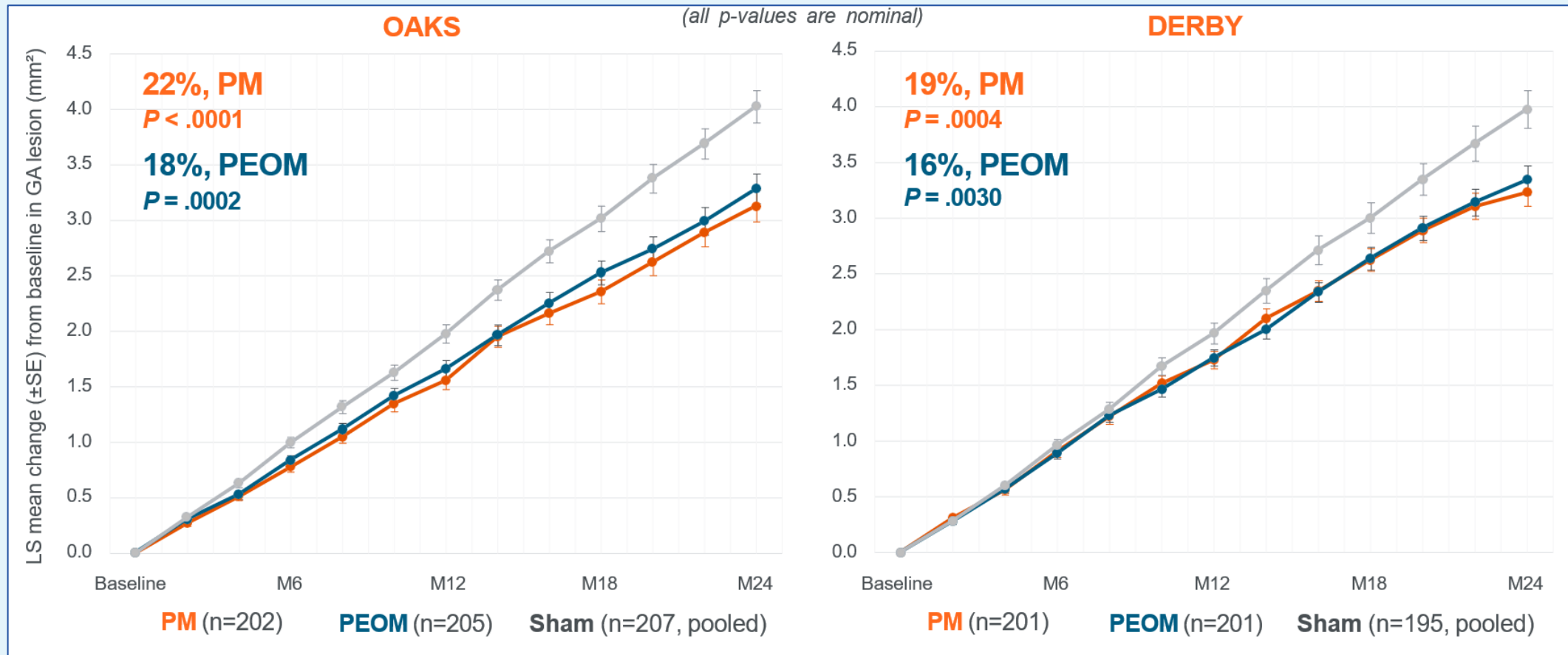
Key Exclusion Criteria

- GA secondary to a condition other than AMD
 - Example: Stargardt disease in either eye
- **CNV** in the study eye (active or history of), including presence of RPE tear (assessed by reading center)

CNV in the fellow eye was not exclusionary

OAKS and DERBY: 24-Month Efficacy

Pegcetacoplan reduced GA lesion growth at month 24

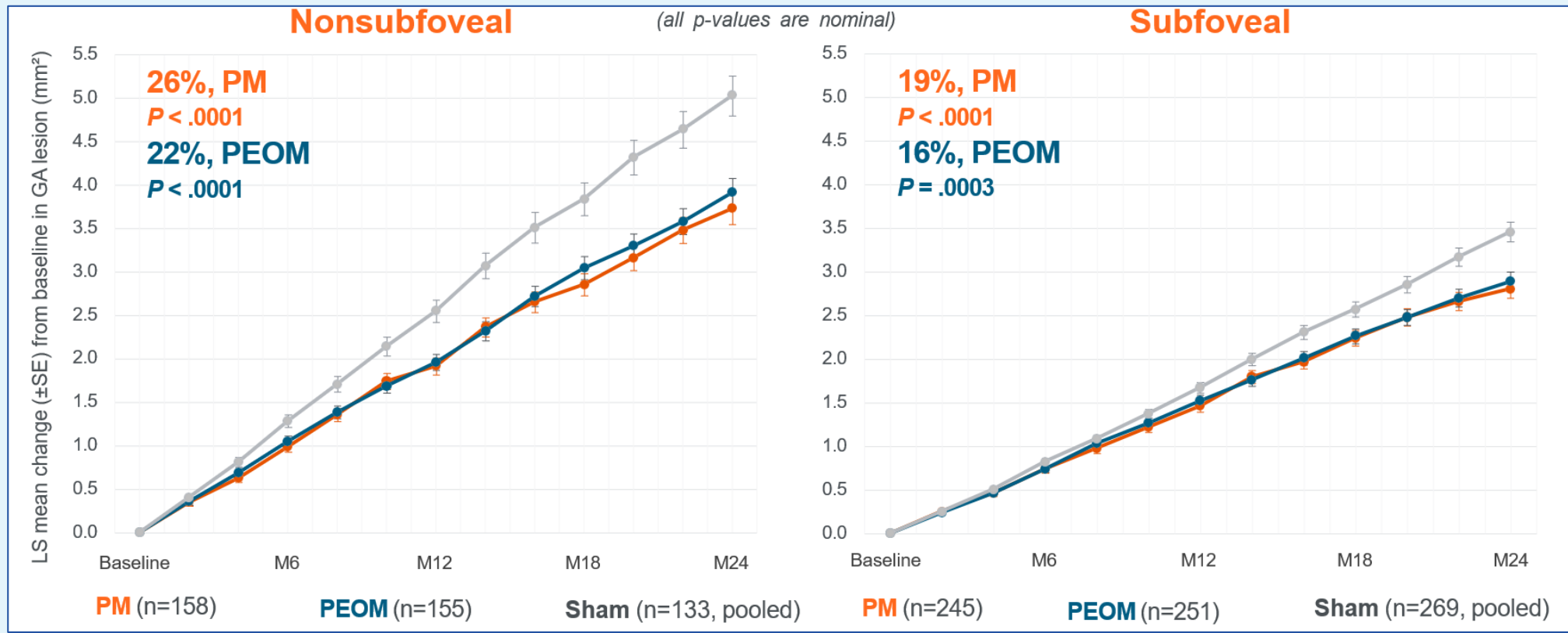


M, month; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly.

Heier J, et al. Presented at: The Retina Society 55th Annual Scientific Meeting; November 2-5, 2022; Pasadena, CA.

OAKS and DERBY Combined: GA Lesion Growth

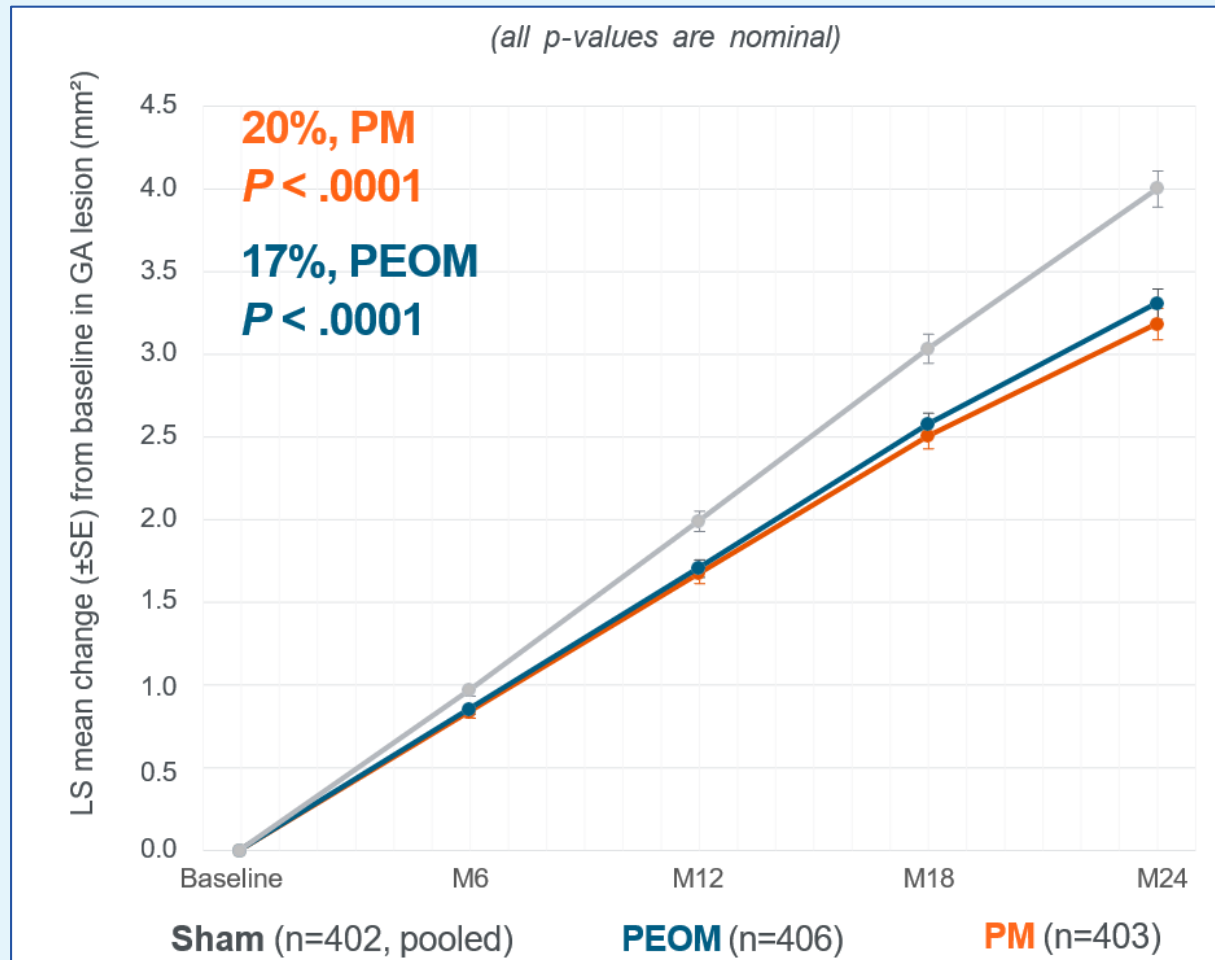
Pegcetacoplan reduced GA lesion growth rate vs sham pooled in lesions with and without subfoveal involvement through month 24



M, month; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly.

Heier J, et al. Presented at: The Retina Society 55th Annual Scientific Meeting; November 2-5, 2022; Pasadena, CA.

OAKS and DERBY Combined: Slope Analysis



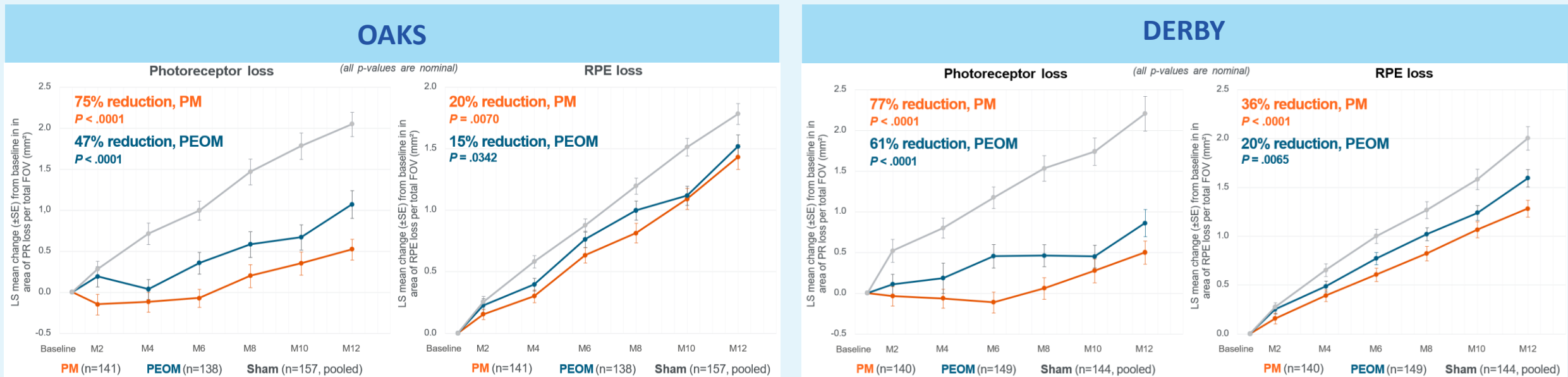
Increased treatment effect over months 18-24:

- PM: 30%
- PEOM: 24%

OAKS and DERBY: PR and RPE Loss

Post hoc analysis of OAKS/DERBY at 12 months using AI-based automated segmentation to map PR and RPE layers

- PR and RPE loss found to be reduced by intravitreal pegcetacoplan

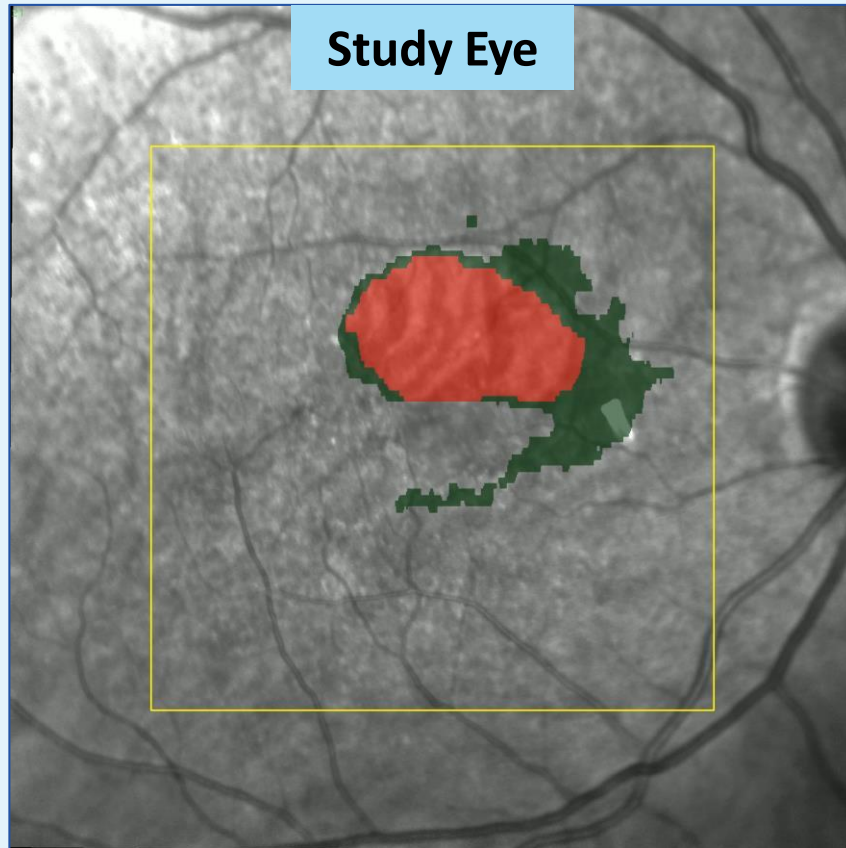


AI, artificial intelligence; PR, photoreceptor.

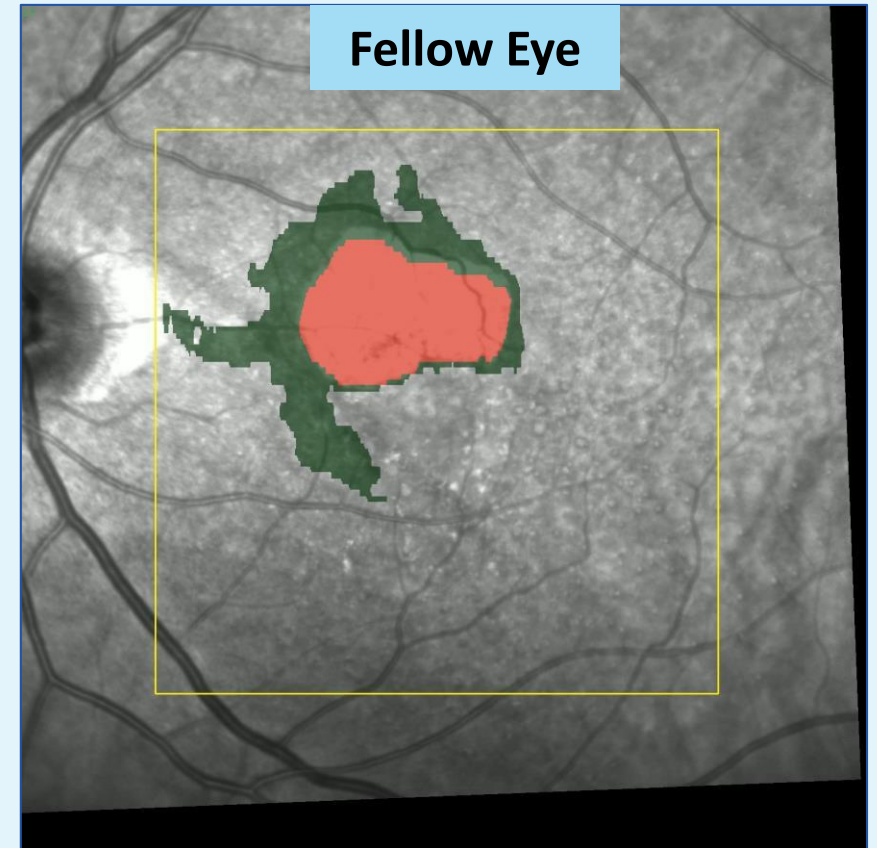
Heier J, et al. Presented at: The Retina Society 55th Annual Scientific Meeting; November 2-5, 2022.

OAKS and DERBY: Treated vs Untreated Eye

Area of RPE loss grew by ~50% in the treated eye and by ~225% in the fellow eye at 12 months



■ PR loss
■ RPE loss



Pegcetacoplan: Safety

- Most important signal was for an increased rate of eAMD in pegcetacoplan-treated eyes
 - Consistent with data through year 1 of OAKS and DERBY, as well as from the phase 2 FILLY study
 - Patients continued study drug treatment during trials and received on-label anti-VEGF therapy at investigator discretion
- IOI also occurred, though more rarely
 - Most cases were mild
 - No cases of vasculitis or retinitis
 - Most patients continued or resumed study drug treatment without IOI recurrence

| | Pegcetacoplan monthly | Pegcetacoplan every other month | Sham |
|---------|--------------------------|------------------------------------|------|
| eAMD, % | 12.2 | 6.7 | 3.1 |
| IOI, % | 3.8 | 2.1 | 0.2 |

Pegcetacoplan – A Discussion



When do you use pegcetacoplan in clinical practice?

What has your experience been?

Avacincaptad Pegol (ACP) Overview

FDA has accepted for Priority Review the NDA for avacincaptad pegol to treat GA secondary to AMD

- Investigational complement C5 protein inhibitor
 - C5 is a key protein within the complement system
 - Maintains integrity of retinal health under normal conditions
- Designed to decrease activation of inflammasomes and the formation of membrane attack complex, preventing or slowing the degeneration of RPE cells
- **PDUFA goal date of August 19, 2023**
- NDA submission based on the 12-month pre-specified primary efficacy and safety results from the GATHER1 and GATHER2 clinical trials

GATHER 1: Phase 2/3 Design (Part 1)

Patients with GA secondary to AMD

Double masked

Part 1: Randomized 1:1:1

ACP 1 mg monthly
(n = 26)

ACP 2 mg monthly
(n = 25)

Sham monthly
(n = 26)

Primary analysis
month 12

Primary endpoint at 12 months

Mean change in GA area from baseline to month 12 (square root transformation)

Descriptive analyses at 18 months

GATHER 1: Phase 2/3 Design (Part 2)

Patients with GA secondary to AMD

Double masked

Part 2: Randomized 1:2:2

ACP 2 mg monthly
(n = 42)

ACP 4 mg* monthly
(n = 83)

Sham monthly
(n = 84)

Primary analysis
month 12

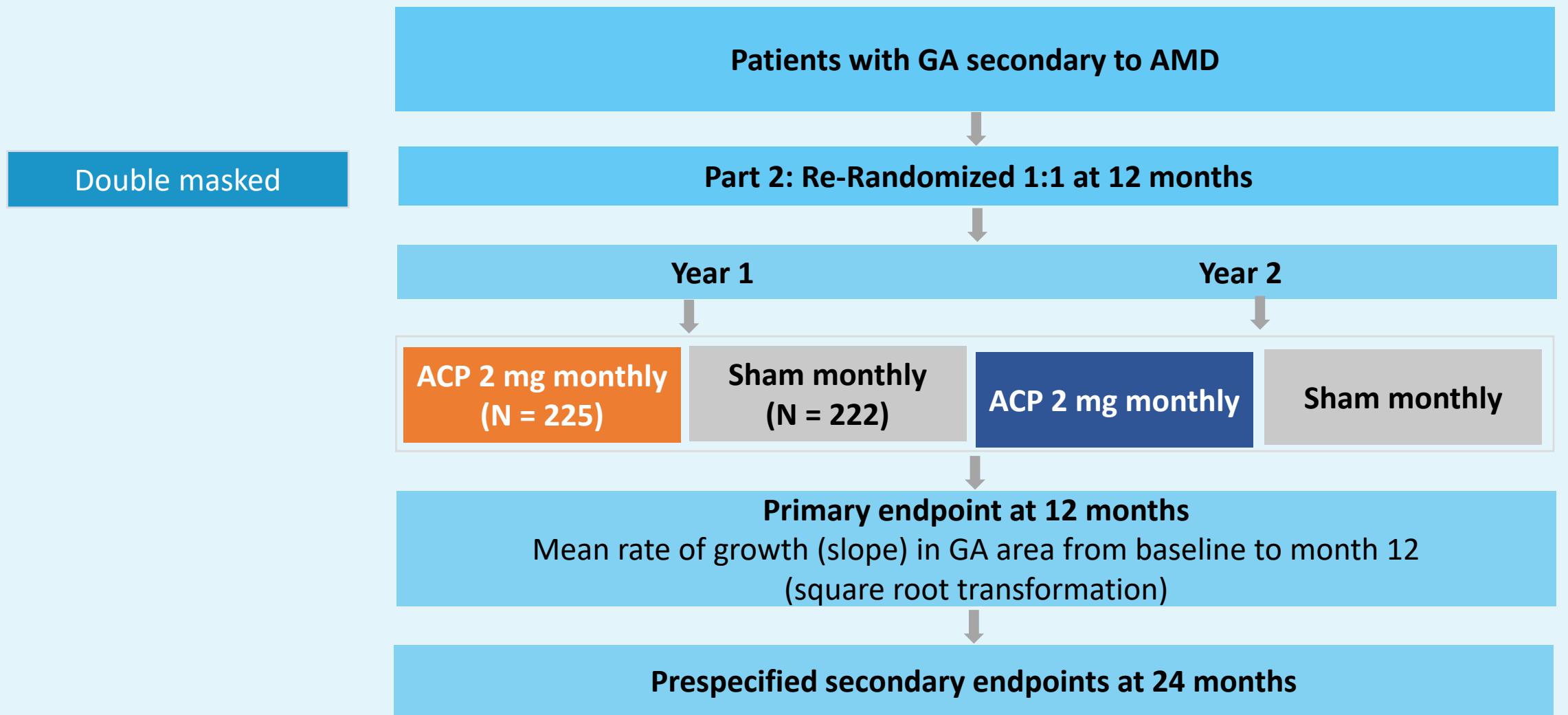
Primary endpoint at 12 months

Mean change in GA area from baseline to month 12 (square root transformation)

Descriptive analyses at 18 months

*2 injections of 2 mg per eye

GATHER 2: Phase 3 Design



Key Inclusion and Exclusion Criteria



Key Inclusion Criteria

- Age \geq 50 years
- BCVA between 20/25 and 20/320
- GA lesion:
 - Non-center point involving
 - GA in part within 1500 μ m from the foveal center
 - Total area between 2.5 mm² and 17.5 mm² (1-7 DA, respectively)
 - If multifocal lesions, \geq 1 lesion had to measure \geq 1.25 mm² (0.5 DA)

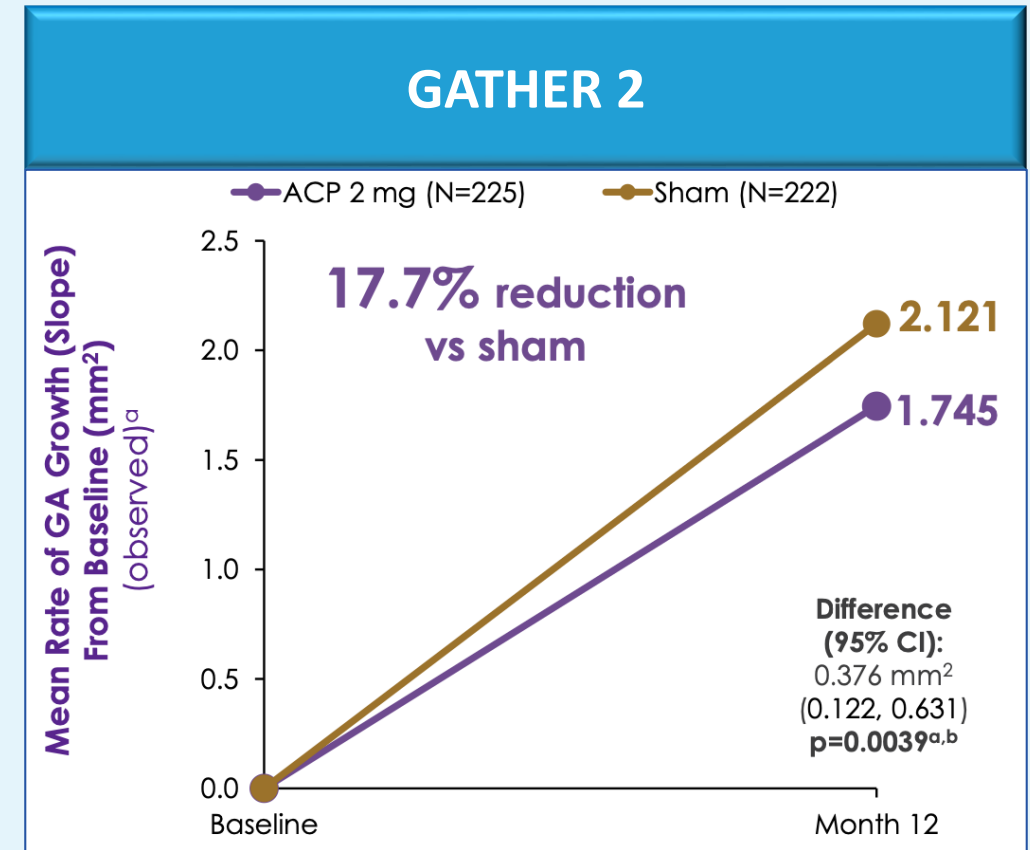
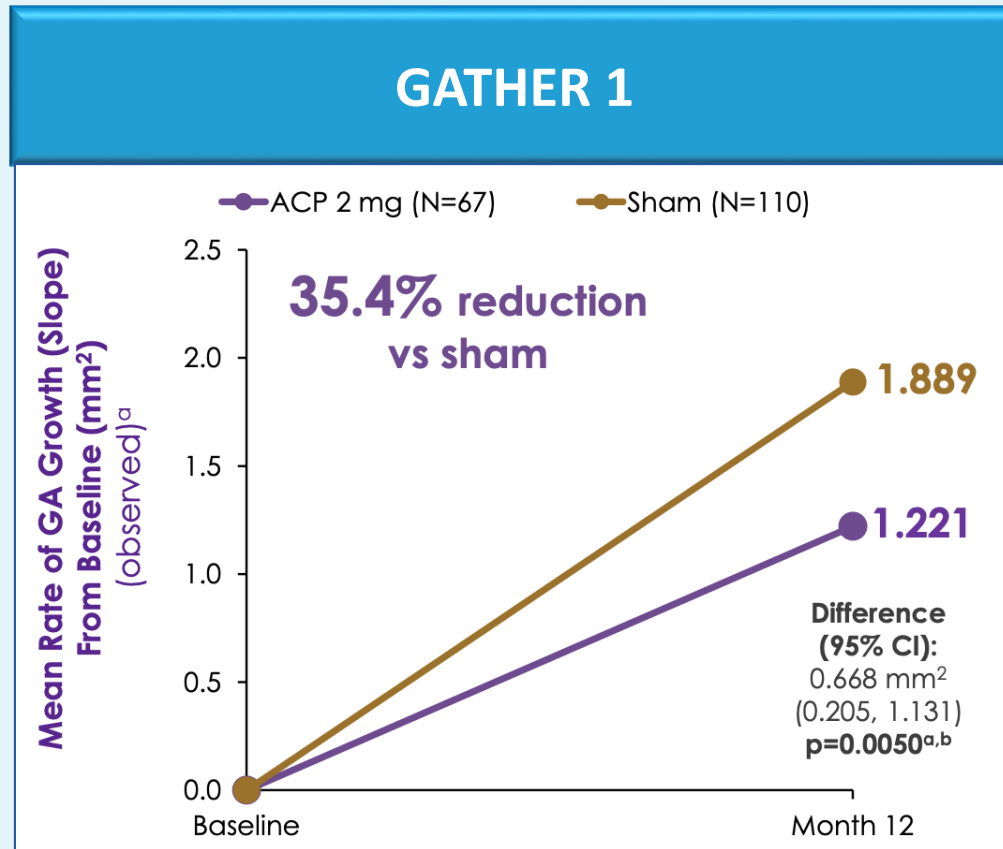


Key Exclusion Criteria

- Evidence of **CNV** in either eye at baseline
- GA secondary to any condition other than AMD in either eye
- Any **prior treatment for AMD** or any **prior intravitreal treatment** for any indication in either eye (except oral vitamin or mineral supplements)
- **Any ocular condition** in study eye **that could progress** during the study and affect central vision or otherwise act as a confounding factor
- Any sign of **diabetic retinopathy** in either eye

GATHER 1 and GATHER 2: Efficacy

Mean rate of observed GA growth (slope analysis) showed consistent efficacy results between the 2 studies^[a,b]



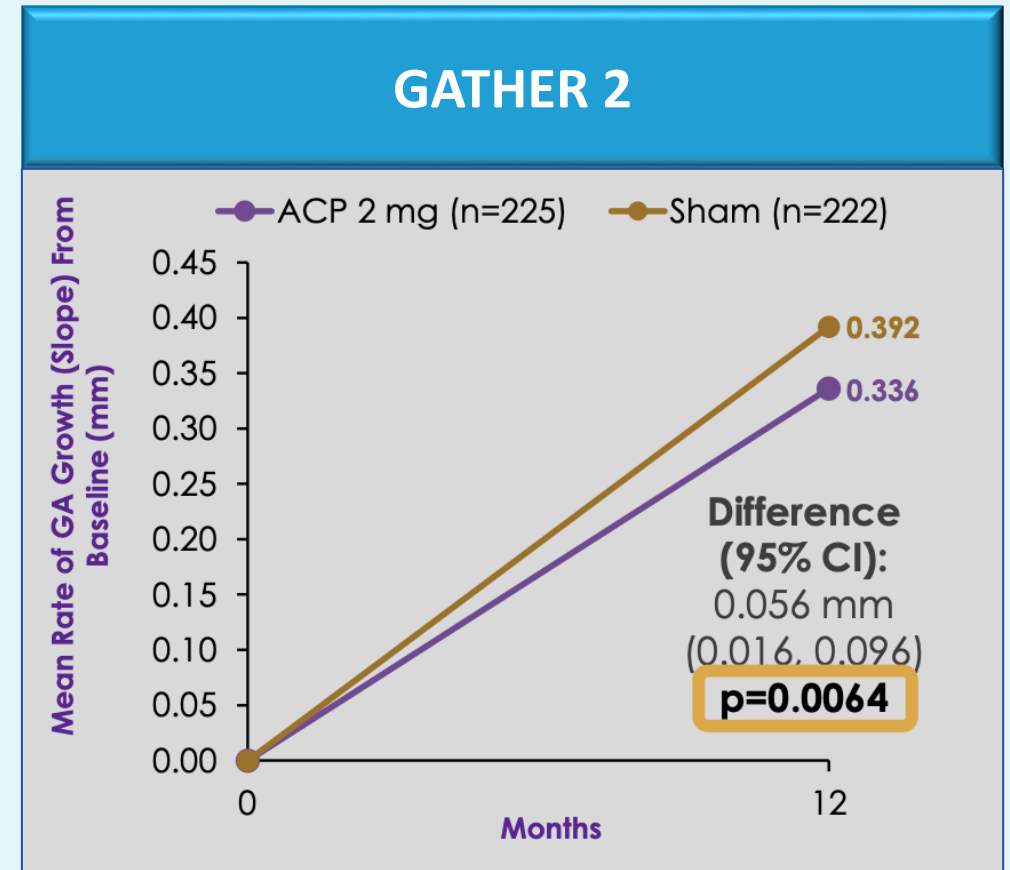
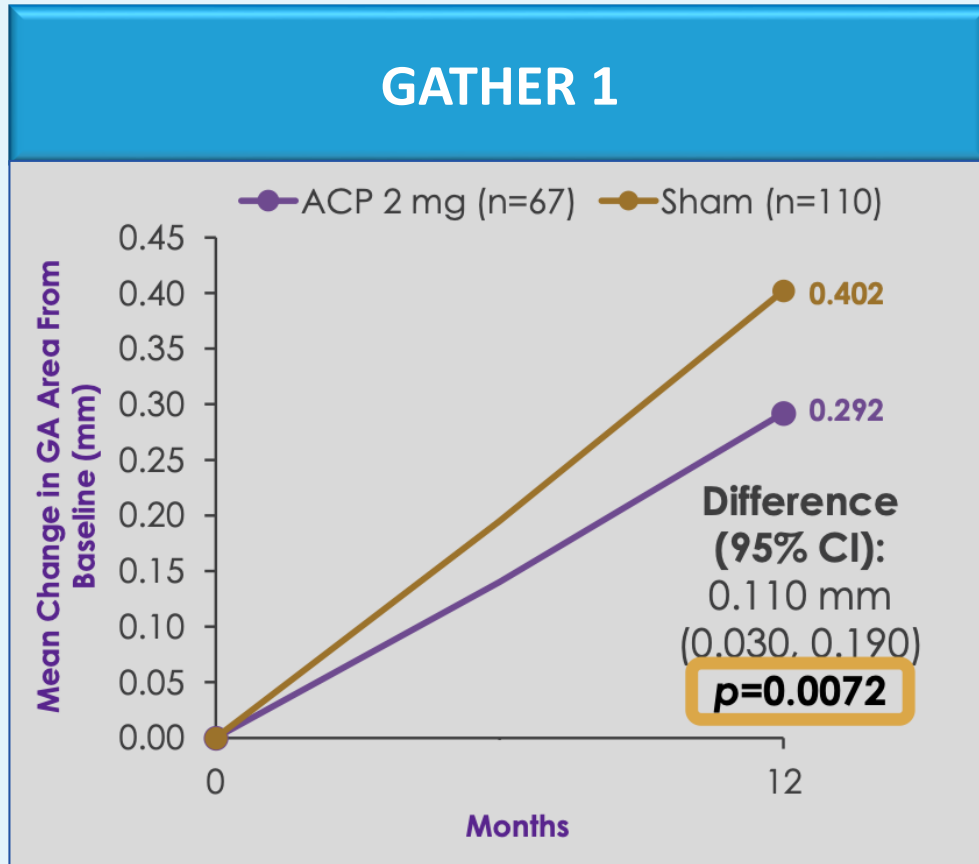
^aNon-square root transformation; ^bDescriptive P value.

CI, confidence interval.

Jaffe GJ, et al. Ophthalmology. 2021;128:576-586; Khanani AM, et al. Presented at: The Retina Society 55th Annual Scientific Meeting; November 2-5, 2022; Pasadena, CA.

GATHER 1 and GATHER 2 Efficacy Results

ACP achieved the 12-month prespecified, primary endpoint, in 2 pivotal, phase 3 studies



ACP: Safety

- Most frequently reported adverse events at 12 months in the 2 mg recommended dose were related to the injection procedure
- There was no ACP-related inflammation, glaucoma, or ocular hypertension

Ocular TRAEs Occurring in $\geq 5\%$ of GATHER 1 Study Participants

| | ACP 2 mg | ACP 4 mg | Sham |
|----------------------------|----------|----------|------|
| Conjunctival hemorrhage, % | 14.9 | 32.5 | 11.8 |
| CNV, % | 9.0 | 9.6 | 2.7 |
| Punctate keratitis, % | 6.0 | 7.2 | 7.3 |
| Increased IOP, % | 6.0 | 19.3 | 0.9 |
| Conjunctival hyperemia, % | 4.5 | 9.6 | 3.6 |
| Conjunctival edema, % | 3.0 | 6.0 | 3.6 |
| Eye pain, % | 3.0 | 7.2 | 2.7 |

IOP, intraocular pressure.

Jaffe GJ, et al. Ophthalmology. 2021;128:576-586.

Use in Clinical Practice – A Discussion



If ACP is approved, how would eyecare providers select between this agent and pegcetacoplan?

Are there any patient subsets that would be better candidates for one vs the other?



Emerging Complement Inhibitors

ANX007

- Antigen-binding fragment of a humanized recombinant monoclonal antibody^[a]
 - Binds to the globular heads of C1q and blocks the downstream activation of the classical complement cascade
- Administered via intravitreal injection^[a-c]
- Phase 2 ARCHER study investigating the efficacy of ANX007 for patients with GA secondary to AMD is ongoing^[b]
 - Enrolled patients with foveal and non-foveal vision loss and an average age of 80 years

ARCHER Topline Results^[c]

- Reduction in rate of GA lesion growth did not reach statistical significance
- ANX007 preserved visual acuity, achieving statistically significant protection against vision loss in both foveal and non-foveal patients through 12 months
- Demonstrated neuroprotective mechanism of protecting photoreceptor cells, synapses, and function

a. Liu Y, et al. [Retina Today](#). Published November/December 2021. Accessed June 15, 2023; b. ClinicalTrials.gov. [NCT04656561](#). Accessed June 11, 2023;

c. Clinical Trials Arena. [Topline Results](#). Published May 25, 2023. Accessed June 15, 2023.

IONIS-FB-L_{Rx}

- Ligand conjugated antisense oligonucleotide targeting complement factor B^[a]
- Administered subcutaneously every 4 weeks^[a,b]
- Phase 2 GOLDEN study is ongoing, but no longer recruiting patients^[b]

GOLDEN Study

- 45-week, placebo-controlled trial evaluating the effect of IONIS-FB-LRx on the rate of change of the area of GA secondary to AMD measured by FAF
- Planned enrollment of 330 patients

2 stages

- Stage 1: Adaptive design in which 3 dose levels will be evaluated in a subset of participants
- Stage 2: After interim analysis of stage 1, the number of participants in 2 of the dose cohorts will be expanded

Danicopan (ALXN2040)

- Investigational, first-in-class inhibitor of complement factor D^[a]
- Phase 2 dose-finding study designed to evaluate the efficacy, safety, and pharmacokinetics of danicopan ongoing
 - Includes screening period of up to 6 weeks, a 104-week masked treatment period, followed by a 30-day follow-up after the last dose
 - 4 treatments arms: 100 mg 2x daily, 200 mg 2x daily, 400 mg 1x daily, and matching placebo
 - Estimated enrollment of 332 participants
 - **Currently recruiting patients**



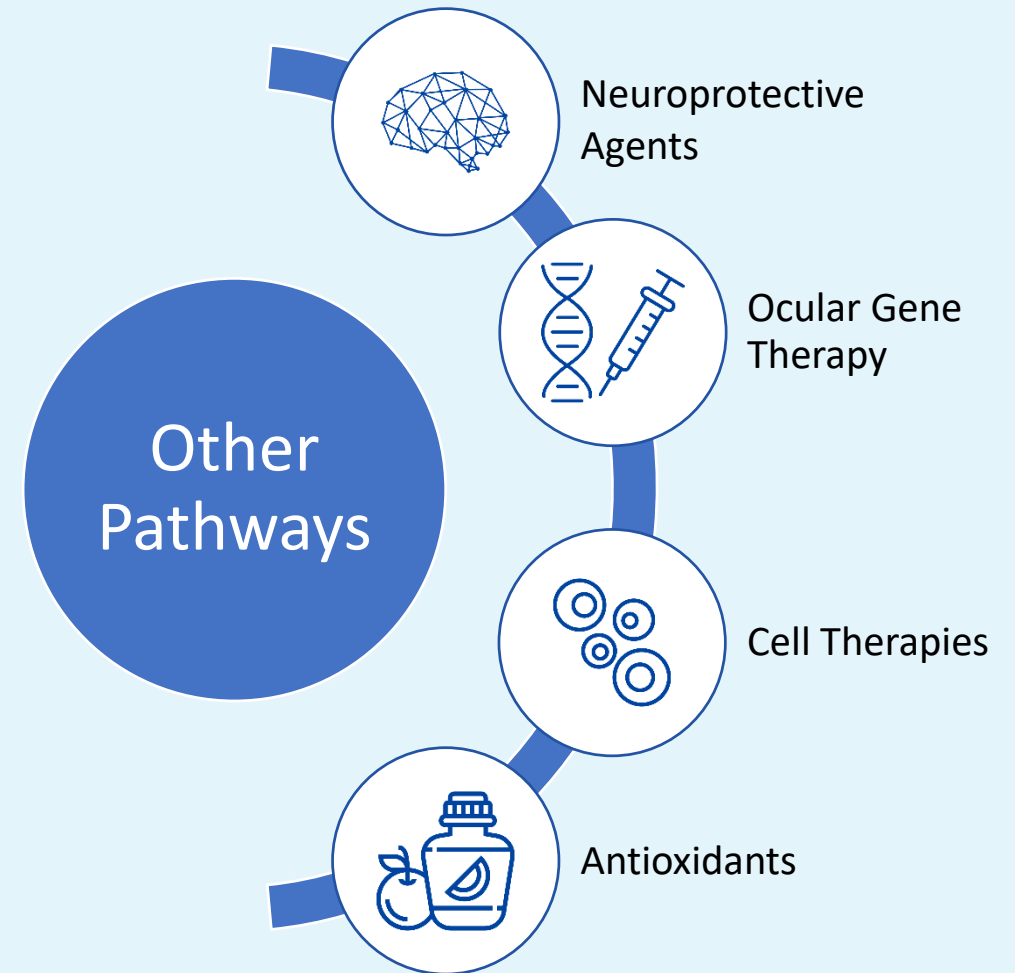
Key Inclusion Criteria

- Vaccination for *Neisseria meningitidis*
- Capable of giving signed informed consent
- Presentation of GA secondary to AMD in ≥ 1 eye
- Entire GA lesion must be $> 1 \mu\text{m}$ outside of the foveal center

Emerging Treatment Pathways

Targeting Unmet Needs With New Pathways

- GA is heterogeneous, varying in appearance and extent between patients^[a]
- **Complement inhibitors** have thus far shown **modest therapeutic effects**^[b]
 - Only a subgroup of patients with GA respond favorably
 - Suggests **complex pathophysiology** of GA
- Many other pathways are currently under exploration^[c]



Rationale for Other Pathways

| Pathway | Rationale |
|--------------------------------------|---|
| Neuroprotective ^[a] | Root cause of vision loss in GA is photoreceptor death; thus, protecting photoreceptors may be an important aspect of treating GA |
| Antioxidants ^[b] | Oxidative stress has been shown to exert cellular damage that leads to eventual retinal and RPE cell atrophy and death; thus, there may be benefit in reducing free radicals in the retina of patients with AMD or GA |
| Cell-based therapies ^[c] | Has potential to regenerate RPE and compromised photoreceptors |
| Ocular gene therapies ^[c] | Has potential to treat GA with a single injection by restoring body's ability to maintain complement system homeostasis |

Antioxidants

ALK-001^[a]

- Modified form of vitamin A
- Administered orally
- Phase 3 SAGA trial
 - Ongoing, not recruiting
 - Evaluating the efficacy and safety of ALK-001 in patients with GA secondary to AMD

AREDS/AREDS2^[b,c]

- AREDS explored oral combination of vitamin E, vitamin C, beta-carotene, zinc oxide, and cupric acid
 - Reduced odds of developing advanced AMD in > 33% of patients with high-risk characteristics
- AREDS2 explored a new oral formulation of lutein, zeaxanthin and omega-3
 - No further significant reduction in the risk of developing advanced AMD

OT-551^[d]

- Antioxidant drop composed of a disubstituted hydroxylamine compound that is converted to the piperidine Tempol-H
 - Tempol-H shown to protect RPE cells from oxidative damage in vitro and photoreceptors from acute light-induced damage in animal models
- No statistically significant differences in structural or functional outcomes were found between study and control eyes

Cell-Based Therapies: OpRegen

- Cell-based product composed of RPE cells derived from human embryonic stem cells^[a]
 - Administered via a single surgery into subretinal space
- Phase 1/2a study findings have been promising^[a]
 - Some patients showed encouraging structural and clinical changes
 - Treatment was well tolerated
- Phase 2 trial ongoing^[b]
 - **Recruiting patients**
 - Estimated enrollment of 60 participants
 - Will deliver dose up to ~200,000 cells into the subretinal space
- Has FastTrack designation^[c]



Inclusion Criteria^[b]

- Ability to undergo a vitreoretinal surgical procedure under monitored anesthesia care
- Diagnosis of GA secondary to AMD
- BCVA score \geq 35 letters and \leq 60 letters in the study eye as assessed by ETDRS
- Pseudophakic (study eye)

Gene Therapy: GT005

- AAV2-based gene therapy aiming to restore complement system homeostasis by increasing complement factor I protein production^[a]
- Administered via transvitreal surgery or via single subretinal injection^[a]
- Phase 1/2 FOCUS trial, phase 2 HORIZON trial, and phase 2 EXPLORE trial are ongoing^[b-d]
 - **EXPLORE is recruiting patients**
 - Evaluating the safety and efficacy (anatomical and functional visual outcomes) of low- vs high-dose GT005 in genetically defined patients with GA due to AMD
 - Trial includes a screening period of up to 8 weeks followed by a 96-week study period
 - Estimated enrollment of 75 patients

FOCUS Interim Data^[e]

- 11 of 13 patients treated with GT005 had increased CFI levels (an average increase of 122% vs baseline) that was sustained at week 29 and beyond
- GT005 was safe and well tolerated
- No serious adverse events

CFI, complement factor I.

a. Stevenson S, et al. [Ophthalmology Times](#). Published February 11, 2022. Accessed June 15, 2023; b. ClinicalTrials.gov. [NCT03846193](#). Accessed June 15, 2023; c. ClinicalTrials.gov. [NCT04566445](#). Accessed June 15, 2023; d. ClinicalTrials.gov. [NCT05019521](#). Accessed June 15, 2023; e. Hepp R. [Retina Today](#). Published May/June 2023. Accessed June 15, 2023.

Emerging Treatments - A Discussion

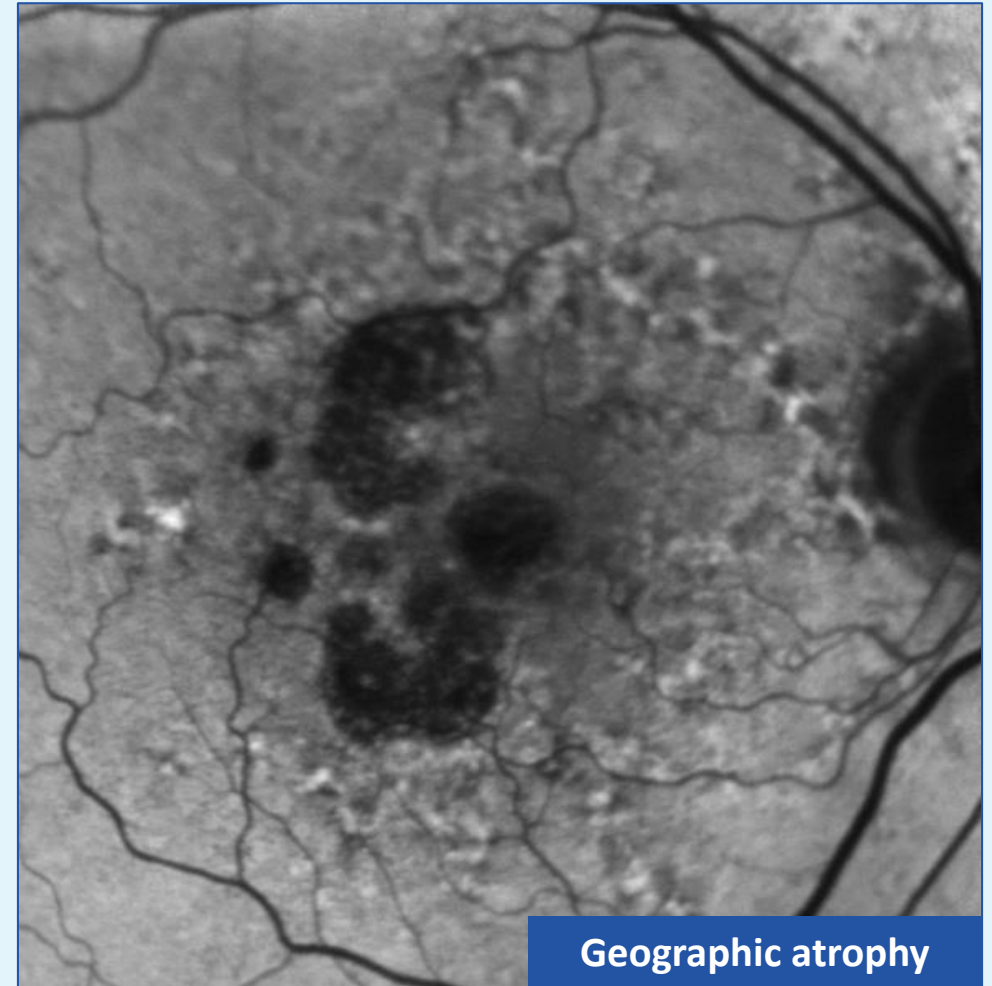


Do any of these pathways seem promising?

**When do you consider enrolling patients
into clinical trials?**

Concluding Remarks

- GA is the advanced form of AMD that is associated with considerable disease burden and progression
- It is a major factor in causing complete vision loss
- Until early 2023, there were no approved pharmacological treatments to prevent or slow the progression of GA, presenting a significant unmet need
- Pegcetacoplan is the first and only approved treatment for GA secondary to AMD but approval of avacincaptad pegol is anticipated
- A number of clinical trials in GA that target the complement system and other pathways are ongoing
- These recent developments signal there is **significant reason for hope in treating GA**



Geographic atrophy



Thank you for participating in this activity.

Please complete the program assessment and evaluation to receive credit.