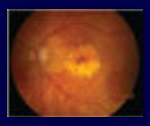
Advancing the Understanding of Geographic Atrophy – 2024



2024

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Faculty & Disclosures

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Disclosures:
Consulting: Allergan, Carl Zeiss, Genentech
Regeneron, Oraxis, Iveric, Avellino, Visus
Advisory Board: Allergan,Carl Zeiss, Genentech, Tarsus
Regeneron
Lecturing fee: Allergan, Carl Zeiss, Regeneron
CE Advisory Board: Reed Exhibitions

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Disclosures: Consultant: 4DMT, Alcon, Alimera, Allergan/AbbVie, Apellis, Aviceda, Bausch + Lomb, Genentech, Inc., Iveric Bio, Regeneron. Research: Janssen.

2

2

Learning Objectives

Upon completion of this activity, the participant should be able to:

1. Describe the role of imaging for detecting and monitoring progression of geographic atrophy (GA).
2. Identify patients who are candidates for GA treatment.
3. Explain how GA treatments target the complement pathway.
4. Review clinical trial evidence supporting efficacy, safety, and injection frequency of GA therapies.

3

3

Overview

- Using advanced technology and algorithms to improve diagnostic accuracy and predict the course of advancing AMD – imaging features associated with progression – optical coherence tomography (OCT), artificial intelligence (AI), and more
- Dysregulation of the complement cascade and its implications in GA pathogenesis
- Review of relevant data from key ophthalmology meetings this past year

4

4

Defining and Assessing Geographic Atrophy

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5

Geographic Atrophy

Responsible for approximately 20% of all cases of legal blindness in North America	Increasing incidence and prevalence owing to a higher life expectancy	Risk factors advanced age, race, smoking, genetics, and diet	One study, smoking > 40 pack-years of cigarettes was associated with a 3.5-fold higher risk for GA

Holz, Frank G., et al. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):1079-1091.

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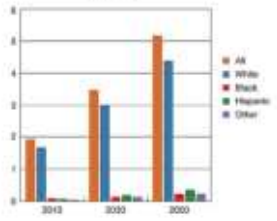
6

The Burden of Age-Related Macular Degeneration (AMD)

PROJECTIONS FOR AGE-RELATED MACULAR DEGENERATION IN 2030 AND 2050 (IN MILLIONS) IN US POPULATION



Nei.nih.gov

7

Late AMD = GA OR Neovascular AMD

Globally, late AMD affects[1]

- 2020: >11 million
- 2040: >18 million

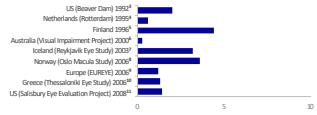
Prevalence increases with age

- From age 50: prevalence quadruples every 10 years of age[2]

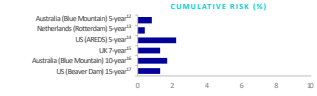
Geographic atrophy

- Accounts for ~35% of late AMD and 20% of legal blindness attributed to AMD[19]

LATE AMD PREVALENCE (%)



CUMULATIVE RISK (%)



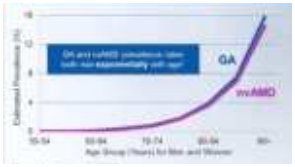
1. Wong WL, et al. *Lancet Glob Health*. 2014;2(2):e106-116; 2. Rudnicka AR, et al. *Ophthalmology*. 2012;119(3):571-580; 3. Klein R, et al. *Ophthalmology*. 1992;99(6):933-943; 4. Vingerling JR, et al. *Ophthalmology*. 1995;102(2):205-210; 5. Hirvelä H, et al. *Ophthalmology*. 1996;103(6):871-877; 6. Vanderwerkt MR, et al. *Ophthalmology*. 2000;107(8):1593-1600; 7. Jonasson F, et al. *Arch Ophthalmol*. 2003;121(3):379-385; 8. Bjönnson OM, et al. *Acta Ophthalmol Scand*. 2006;84(5):626-643; 9. Augood CA, et al. *Arch Ophthalmol*. 2006;124(4):529-535; 10. Topouzis F, et al. *Am J Ophthalmol*. 2006;142(6):1076-1079; 11. Bressler SB, et al. *Arch Ophthalmol*. 2008;126(2):241-245; 12. Mitchell P, et al. *Ophthalmology*. 2002;109(6):1092-1097; 13. van Leeuwen R, et al. *Arch Ophthalmol*. 2003;121(4):519-526; 14. Davis MD, et al. *Arch Ophthalmol*. 2005;123(11):1484-1498; 15. Sparrow JM, et al. *Eye (Lond)*. 1997;11(Pt 3):315-324; 16. Wang JJ, et al. *Ophthalmology*. 2007;114(1):92-98; 17. Klein R, et al. *Ophthalmology*. 1997;104(1):7-21; 18. Rudnicka AR, et al. *Am J Ophthalmol*. 2015;160(3):85-93.e3. 19. Gemenetzi M, et al. *Eye (Lond)*. 2016;30(1):1-16.

8

Prevalence of GA - Currently Affects >5 Million People Worldwide

THE AGING POPULATION WILL INCREASE THE GLOBAL BURDEN OF GA AS MUCH AS nvAMD[1]

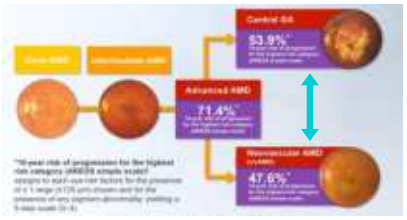
ESTIMATED PREVALENCE OF GA AND NVAMD ARE SIMILAR FOR CAUCASIANS IN THE US[1]



Wong WL, et al. *Lancet Glob Health*. 2014;2(2):e106-e116; Rudnicka AR, et al. *Am J Ophthalmol*. 2015;160(1):85-93.e3.

9

The 10-year Risk of Developing nAMD and Central GA Is Similar[1]



AREDS = Age-Related Eye Disease Study.
1. Chew EY, et al. *JAMA Ophthalmol*. 2014;132(3):272-277; 2. Ferris FL, et al. *Arch Ophthalmol*. 2005;123(11):1570-1574.

10

Quality of Life is Affected by Dry AMD and GA

Sports
Less exercise
Less engagement with friends

Household Chores
Less social interactions, unsure of a clean house

Personal Hygiene
Too much effort to prepare for outing; social isolation

Reading
Loss of reading as a hobby

Transportation
Isolation from family and friends
Reliance on others

Need for Aids
Need to carry magnifiers at all times

Nielsen JS, Singh AP, Patel SS, et al. How much do we know about the economic and patient-reported burden of geographic atrophy? Talk presented at EURETINA 2016, Copenhagen, September 11, 2016. Accessed November 29, 2016.

11

Patients with GA Experience Poor Vision-Related Quality of Life

AMONG PATIENTS WITH GA WHO HAD A DRIVER'S LICENSE:

said they did not feel confident driving during the day

AND

said they did not feel confident driving at night

of those with GA reported a worsening of vision over the past year

VS

of controls (OR 13.55; $P < .001$)

OR=odds ratio
Patel PJ, et al. *Clin Ophthalmol*. 2020;14:15.

12

How do we measure GA?

- **Visual acuity** – Low Luminance, Reading Speed
- **Near Infrared Imaging**
- **Color fundus photography**
- **Fundus autofluorescence**
- **OCT** – spectral domain and swept source
- **Artificial intelligence enabling**

13

BCVA is Not a Reliable Measure

BCVA does not correspond directly to GA lesion enlargement due to possible foveal sparing

BCVA often underrepresents vision loss

Alternative assessments:
Low-luminance visual acuity (LLVA)/ Low luminance deficit (LLD)
Reading speed assessments
Microperimetry
Patient-reported outcomes

Nassisi M et al. OCT risk factors for development of late age-related macular degeneration in the fellow eyes of patients enrolled in the HARBOR Study. *Ophthalmology*. 2019.

14

14

Low Luminance

GA patients have significant impairment in dimly lit environments

Low-luminance visual acuity (LLVA) is measured by placing a 2.0-log unit neutral density filter over the best correction for the eye and having the participant read the normally illuminated ETDRS chart

Low-luminance deficit (LLD) is the difference between regular VA and LLVA

In one study, the baseline low-luminance deficit in visual acuity was a strong predictor of subsequent VA loss for all levels of baseline visual acuity in GA patients

Sunness, Janet S., et al. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. *Ophthalmology*. 2008;115 (9):1480-1488.

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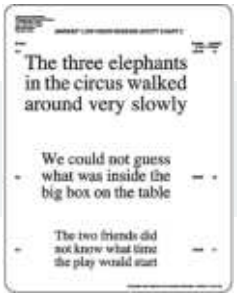
Reading Speed

A single letter may still fit into a small preserved foveal region

A single sentence read by a patient likely will hide within parafoveal atrophic areas



Lindner, Moritz, et al. Determinants of reading performance in eyes with foveal-sparing geographic atrophy. *Ophthalmol Retina*. 2019;3(3):201-210.

16

16

Color Photos for Atrophy Quantification

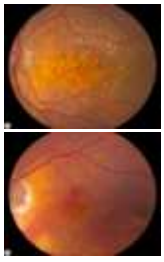
Definition of GA by color imaging:

- Sharply demarcated borders
- Depigmentation
- Increased visibility of choroidal vessels

CONS

- Requires good stereopsis for reliable determination of the borders for quantification
  - Insufficient contrast
- Not always practical in all patients and in the context of large trials
- Requires more chair time in single modality device

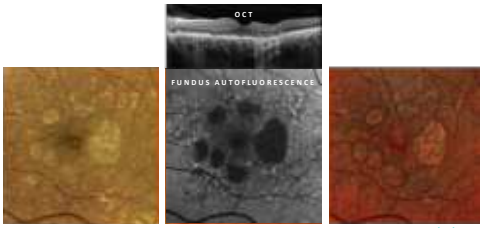
DOESN'T ALWAYS HAVE "CLASSIC" GEOGRAPHIC APPEARANCE



Holz FG, et al. *Ophthalmology*. 2017;124(4):464-478.
Images courtesy of Caroline R. Baumal, MD, FASRS

17

What About Other Imaging Approaches to GA?



CONFOCAL WHITE LIGHT (Eidon) | FLASH WHITE LIGHT (Kowa) | CONFOCAL SLO (IR) (Heidelberg)

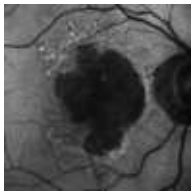
Courtesy of Giovanni Staurenghi

18

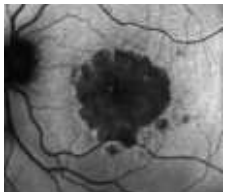
18

GA on Blue Light FAF

GA is readily identified as large patches of decreased autofluorescence on scanning laser ophthalmoscopy image



Enlargement of GA on FAF has been key outcome measure in clinical trials



ONE OF THE MOST IMPORTANT APPLICATIONS OF FAF

Images courtesy of Caroline R. Baumal, MD, FASRS

19

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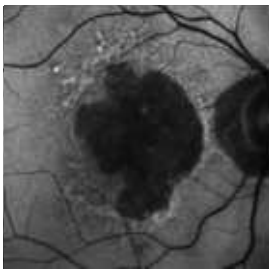
GA on Blue Light FAF

ONE OF THE MOST IMPORTANT APPLICATIONS OF FAF

Enlargement of GA on FAF has been key outcome measure in clinical trials



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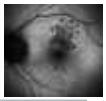
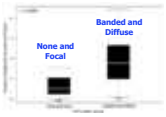
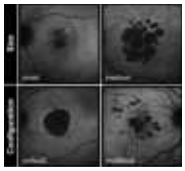
Patterns of Abnormal FAF in Eyes With GA

TRICKLING
Fastest growth!



- Larger lesions and multifocal lesions grow faster
- Why?
  - Larger perimeter





Bindewald A, et al. *Br J Ophthalmol*. 2005;89(7):874-876.

21

21

Progression

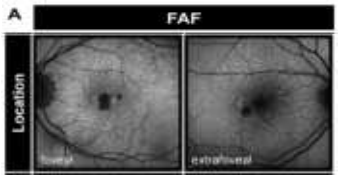
EXTRAFOVEAL GA LESIONS SHOW FASTER PROGRESSION THAN FOVEAL LESIONS.[1]

GA Progression Study:

- Significantly greater progression rate of extrafoveal (2.05 mm²/y) vs foveal lesions (1.28 mm²/y) *P*=.0012

FAM Study:

- Progression toward the periphery 2.8-fold faster than progression toward the fovea[3]



FAM = fundus autofluorescence imaging in age-related macular degeneration.
1. Fleckenstein M, et al. *Ophthalmology*. 2018;125(3):369-390. Open access under a Creative Commons BY-NC-ND license. 2. Schmitz-Valckenberg S, et al. *Ophthalmology*. 2016;123(2):361-368. 3. Lindner M, et al. *Ophthalmology*. 2015;122(7):1356-1365.

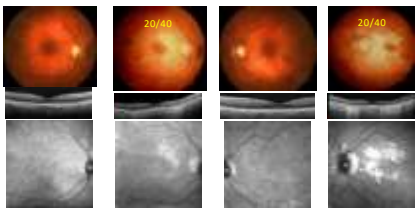
22

22

Case Presentation

INCIDENCE OF GA IS 0.81% IN 40S INCREASES TO 3.5% IN PATIENTS OLDER THAN 75 [1,2]

63-Year-old white female returns after 10 years now 73 with visual complaints and seeking help!



Images and Case Courtesy of Mohammad Rafieetary, OD
Charles Retina Institute

1. Friedman DS, et al. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol*. 2004;122(4)
2. Sunness JS. The natural history of geographic atrophy, the advanced atrophic form of age-related macular degeneration. Mol Vis. 1999 Nov 3;5

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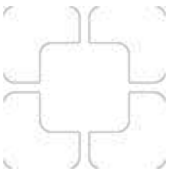
23

What About OCT?

MORE COMFORTABLE THAN FAF

UBIQUITOUSLY AVAILABLE



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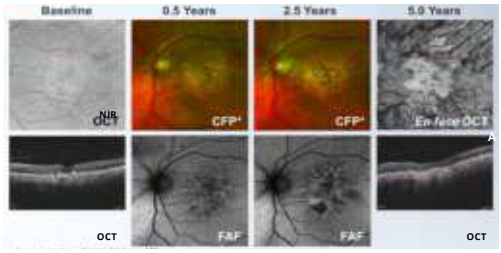
24

Multimodal Imaging Is most helpful



Images courtesy of John Kitchen, MD.
*Color fundus photos (high-definition digital images termed optomap) were captured on an Optos instrument.
1. Göbel AP, et al. Ophthalmologica. 2011;226(4):182–190. 2. Khanifar AA, et al. Retina. 2012;32(9):1884–1891.

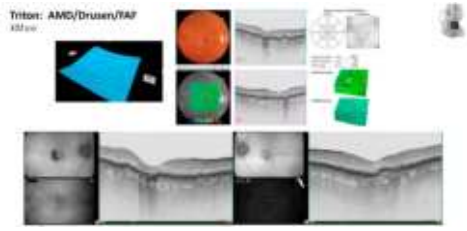
25

Combined Imaging Device

Swept Source OCT with Fundus Camera (Topcon Triton)

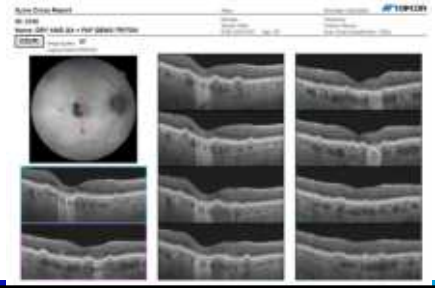
26

Combined Imaging Device – Fundus/ SS OCT



27

Combined FAF, SS OCT



28

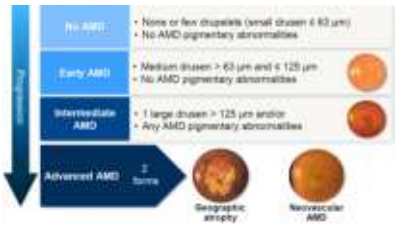
Artificial Intelligence enables mapping of photoreceptors and RPE cells

- Detection of early conversion
- Monitoring disease activity and progression
- Quantification of the therapeutic response
- Ratio of PR/RPE loss as an important predictor
- Confirmation of phase III trials

29

29

AMD Classification



Ferris et al. Ophthalmology. 2013; 120(4):844-851.

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30

Consensus Definitions and New Terminology for Geographic Atrophy on OCT

Complete RPE + outer retinal atrophy
- **GA is a subset** of this (which excludes the region of presumptive CNV)

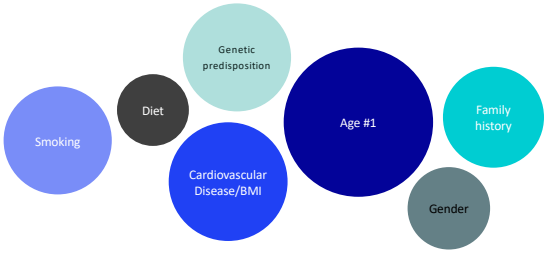
MUST HAVE ALL 3 of the following:
1. Hypertransmission of ≥250 micrometers
2. Zone of attenuation/disruption of RPE+/-basil lamina complex of ≥250 micrometers
3. Evidence of overlying photoreceptor degeneration whose features include the outer nuclear layer thinning, external limiting membrane loss, and ellipsoid zone (EZ)/interdigitation zone loss

CAN'T HAVE: SCROLLED RPE OR OTHER SIGNS OF RIP

Sadda SR, et al. *Ophthalmology*. 2018;125(4):537–548. Images courtesy of Caroline R. Baumal, MD, FASRS

31

Risk Factors for Advanced AMD and GA



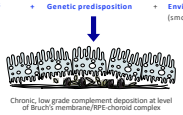
Brown DM, Regillo CD, Pieramici DJ; Updates in the management of geographic atrophy in dry age-related macular degeneration, http://www.medscape.org/viewarticle/865061, Released: 12/14/2015, Accessed November 20, 2016.
Facts about age-related macular degeneration. NEI website, https://nei.nih.gov/health/maculardegen/armd_facts. Reviewed: September 2015, Accessed November 20, 2016.

32

32

Complement Hypothesis in Pathogenesis of AMD

Lifelong oxidative stress (light, oxygen, lipids, retinoids, CEP haptens) + **Genetic predisposition** + **Environment** (smoking, diet, infection)



Chronic, low grade complement deposition at level of Bruch's membrane/RPE-choroid complex

Complement-mediated damage to Bruch's membrane + VEGF expression leads to CNV

Continuous low-grade complement-mediated inflammation leads GA

CEP = carboxyethylpyrrole; CNV = choroidal neovascularization.
Age-Related Eye Disease Study Research Group. *Arch Ophthalmol*. 2001;119(10):1417-1436; Ambati J, et al. *Nat Rev Immunol*. 2013;13(6):438-451; Ricklin D, et al. *Immunol Rev*. 2016;274(1):33-58. Images courtesy of Caroline R. Baumal, MD, FASRS

33

33

Biochemical Composition of Drusen

OTHER PROTEINS
Apolipoprotein B100, E
Amyloid beta

Lipids	• Cholesterol • Phospholipids
Matrix proteins	• Various collagens • (Types I, III, IV, VI, and others) • TIMPs and MMPs • Vitronectin • Fibronectin
Inflammatory proteins	• Complement • Others
Serum proteins	• Albumin • Immunoglobulins

MMP = matrix metalloproteinase; TIMP = tissue inhibitors of metalloproteinase.
Hageman GS, Mullins RF. *Mol Vis*. 1999;5:28.

34

34

Complement and AMD

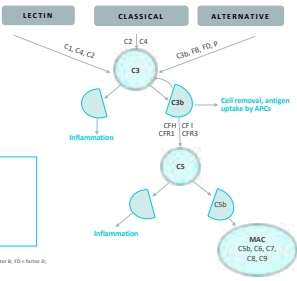
- The COMPLEMENT SYSTEM is first line of defense of the immune system
- It protects us from microorganisms
- It constitutes our innate immunity, which is not adaptable and does not change as we age
- Activated by the adaptive immune system (through antigen antibody interaction)

35

35

Complement Cascade

- **Complement system and AMD**
- **1st line** defense of immune system
- Protection from microorganisms
- *innate immunity*
  - Not adaptable
  - Does not change as we age
- Activated by *adaptive immune system* (through antigen antibody interaction)



3 Separate Pathways
- Activation
- Converge on C3

Classical: antigen-antibody complexes

Lectin: polysaccharides on microorganisms

Alternative: pathogen cell surfaces and nonspecific/ spontaneous activation

APC = antigen presenting cell; CF = complement factor; FB = factor B; FD = factor D; MAC = membrane attack complex.
Adapted from Ricklin D, et al. *Immunol Rev*. 2016;274(1):33-58.

36

36

Data Implicating Complement Dysfunction and AMD

Genetic association studies: genome-wide association studies (GWAS)

Local complement activation in AMD

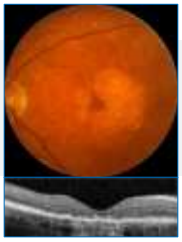


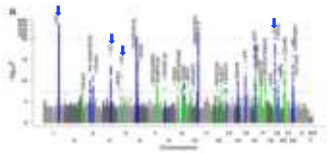
Image courtesy of Caroline R. Baumal, MD, FASRS

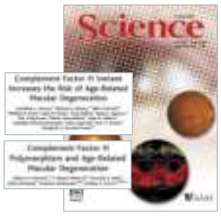
37

37

Genetics and AMD

- >40 loci implicated
- Account for ≈50% of risk
- Complement components: CFH, CFI, C3, C9, C2/CFB
  - Variants predicted to increase activation or decrease inactivation of complement cascade → increased inflammatory activation





Haines JL, et al. *Science*. 2005;308(5720):419-421; Edwards AO, et al. *Science*. 2005;308(5720):421-424; Handa JT, et al. *Nat Commun*. 2019;10(1):3347; Fritsche LG, et al. *Nat Genet*. 2016;48(2):134-143.

38

38

Data Implicating Complement Dysfunction and AMD Complement Activation in AMD Eyes

- Histopathologic studies of AMD eyes
- Confocal immunofluorescence microscopy:
  - C3 and C5 accumulation in drusen and sub-RPE space

(A) Arrowheads indicate cross-sections of choroidal capillaries; (B) Arrowheads indicate C3 immunoreactivity is also present in the extracellular space between the RPE and Bruch's membrane and in the cytoplasm of some RPE cells. BM = Bruch's membrane; Chor = choroid; Dr = drusen; PR = photoreceptor layer.
Anderson DH, et al. *Prog Retin Eye Res*. 2010;29(2):95-112; Anderson DH, et al. *Am J Ophthalmol*. 2002;134(3):411-431.

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Summary

- GA is a prevalent disease impairing visual acuity
- Multimodal imaging is helpful In Geographic Atrophy with each of their own benefits
- Alternative complement activation is a underlying mechanism of geographic atrophy

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Therapies Targeting Geographic Atrophy

Rishi P. Singh, MD, FASRS

41

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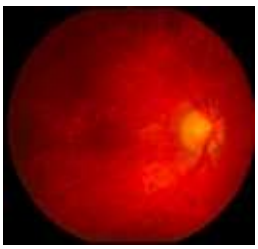
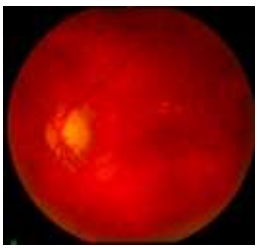
67F with mild blurry vision OU





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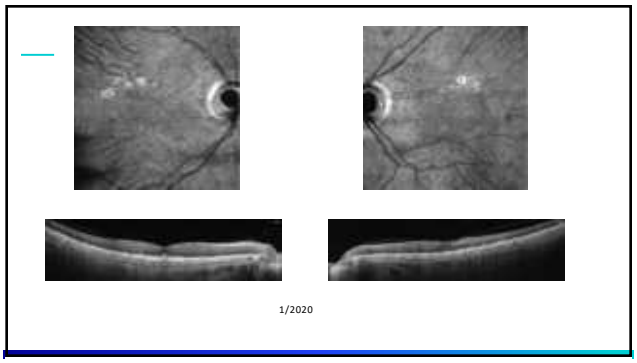

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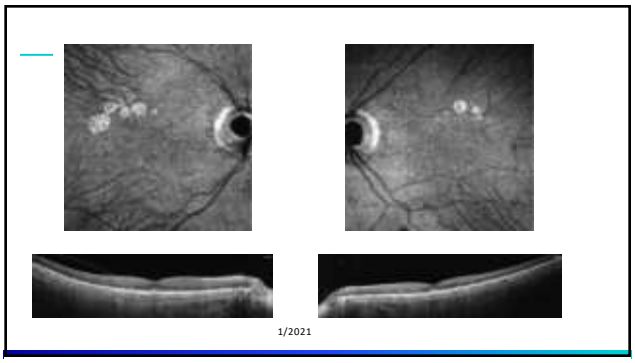

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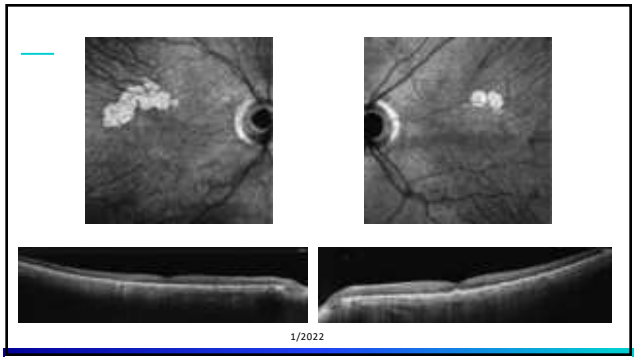

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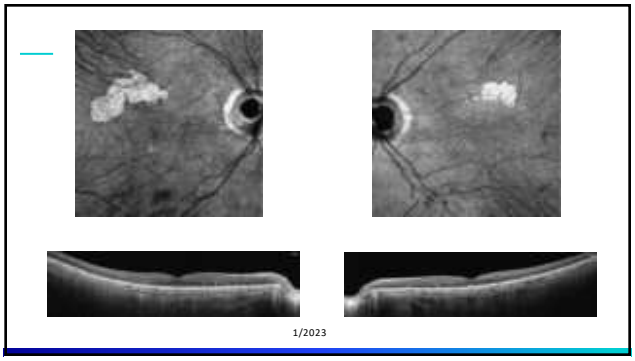

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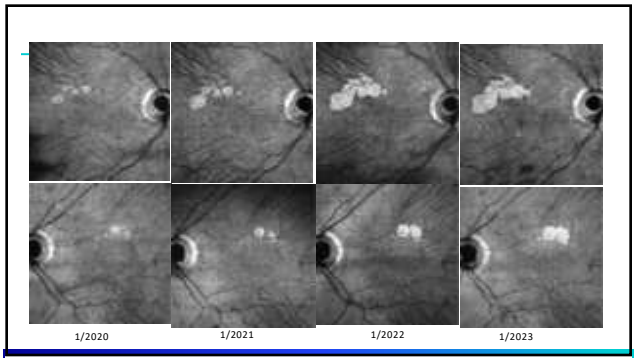

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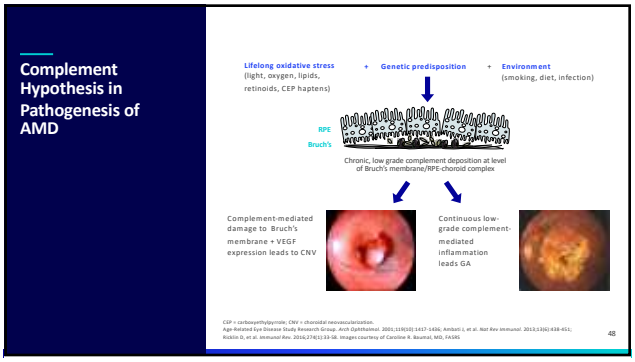


48

Complement and AMD

- The COMPLEMENT SYSTEM is first line of defense of the immune system
- It protects us from microorganisms
- It constitutes our innate immunity, which is not adaptable and does not change as we age
- Activated by the adaptive immune system (through antigen antibody interaction)

49

49

Complement Cascade

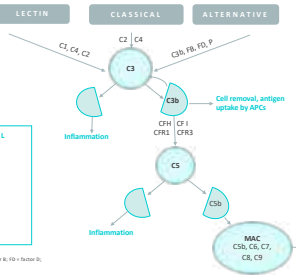
- **Complement system and AMD**
- **1st line** defense of immune system
- Protection from microorganisms
- *innate immunity*
  - Not adaptable
  - Does not change as we age
- Activated by *adaptive immune system* (through antigen antibody interaction)

FOR DETECTION AND REMOVAL FOREIGN PATHOGENS

-30 proteins

Activation

- Inflammation
- Opsonization/phagocytosis
- MAC-mediated lysis, cell secretion, proliferation



3 Separate Pathways
- Activation
- Converge on C3

Classical: antigen-antibody complexes

Lectin: polysaccharides on microorganisms

Alternative: pathogen cell surfaces and nonspecific/ spontaneous activation

APC = antigen-presenting cell; CF = complement factor; FB = factor B; FD = factor D; MAC = membrane attack complex.
Adapted from Ricklin D, et al. *Immunol Rev.* 2016;274(1):33-58.

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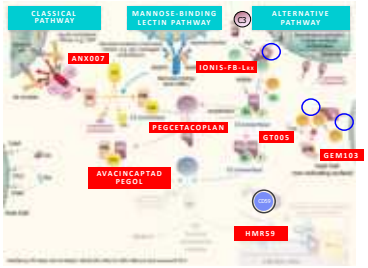
Complement Inhibition in Dry AMD

EXAMPLES OF EMERGING THERAPIES



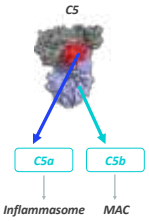
Ag-Ab = antibody-antigen; CRP = C-reactive protein; MASP = Mannose-associated serine protease.

51

51

C5 Activation

- C5a is a priming agent for inflammasome activation in RPE cells
- C5a upregulates inflammasome-related genes
- Inflammasome activation increases levels of IL-1β and IL-18 (both induce RPE degeneration)
- NLRP3 inflammasome, IL-1β, and IL-18 are present in postmortem eyes with geographic atrophy secondary to dry AMD
- C5b causes MAC formation
- Lipofuscin component bisretinoid A2E prevents clearance of MAC in RPE cells, leading to accumulation and inducing mitochondrial damage and cell death



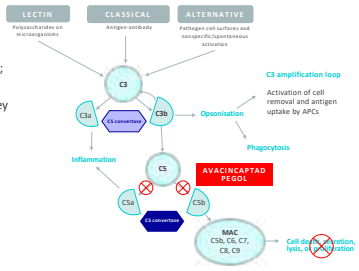
IL = interleukin; NLRP3 = NOD-, LRR- and pyrin domain-containing protein 3.
Desai D, Dugel PU. *Eye (Lond).* 2022;36(2):294-302.
Jaffe GJ, et al. *Ophthalmology.* 2021;128(4):576-586.

52

52

Avacincaptad Pegol (ACP)

- Pegylated RNA aptamer
- Potent/specific inhibitor of complement C5; inhibits C5 cleavage
- Cascade inhibition prevents formation of key terminal fragments regardless of the initial activation pathway



Desai D, Dugel PU. *Eye (Lond).* 2022;36(2):294-302.
Jaffe GJ, et al. *Ophthalmology.* 2021;128(4):576-586.

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53

Avacincaptad Pegol Phase 2/3 Study

- Reduction in mean GA growth rate over 12 months compared with corresponding sham cohorts

Dose	Reduction	*P* value
2 mg	27.4%	.0072
4 mg	27.8%	.0051

- Generally, well tolerated
  - No drug-related AEs or inflammation
  - No ocular SAEs and no cases of endophthalmitis

SAE = serious adverse event.
Jaffe GJ, et al. *Ophthalmology.* 2021;128(4):576-586.

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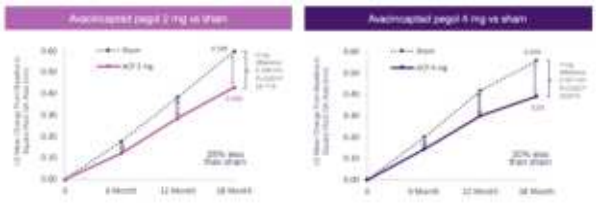
M18 Result Consistent With Primary M12 Endpoint

MEAN RATE OF GROWTH IN GA AREA AS MEASURED BY SQUARE ROOT TRANSFORMATION OVER 12 MONTHS



Based on LS MEANS from MRM model; ITT population Hochberg procedure was used for significance testing; prespecified and descriptive analysis. These least squares means are estimates of the MRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2, and should not be interpreted as directly observed data. *18-month P values are descriptive in nature.
Sheth V. *Invest Ophthalmol Vis Sci.* 2021;62(8):333.

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Safety Results

- Avacincaptad pegol was well-tolerated after 18 months of continuous administration
- No reported avacincaptad pegol-related inflammation
- The most frequently reported ocular AEs were related to the injection procedure[a]

INCIDENCE OF STUDY EYE CNV:

n (%)	12 months	18 months
Sham	3 (2.7%)	3 (2.7%)
ACP 1 mg	1 (4.0%)	2 (7.7%)
ACP 2 mg	6 (9.0%)	8 (11.9%)
ACP 4 mg	8 (9.6%)	13 (15.7%)

[a] Based on investigator-reported safety events.
Sheth V. *Invest Ophthalmol Vis Sci.* 2021;62(8):333.

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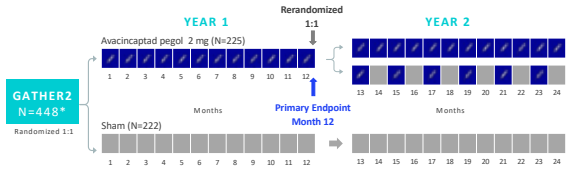
GATHER2

RANDOMIZATION AND TRIAL DESIGN



Primary Endpoint
Mean rate of growth (slope) in geographic atrophy area from baseline to month 12 (square root transformation)

Khanani A, et al. Presented at: AAO 2022. September 30-October 2, 2022; Chicago, IL.

57

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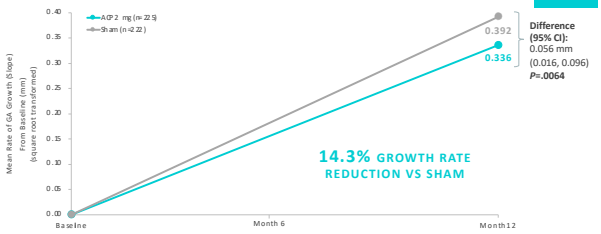
GATHER2 Results

PRIMARY ENDPOINT

NEW DATA!



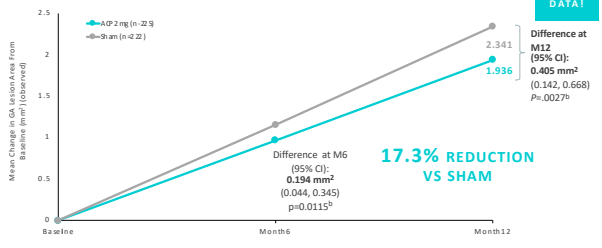
Khanani A, et al. Presented at: AAO 2022. September 30-October 2, 2022; Chicago, IL.

58

58

Mean Change From Baseline Analysis in GA Lesion Area[1]

NEW DATA!



[a]non-square root transformation; [b]Descriptive p-value
Khanani A, et al. Presented at: AAO 2022. September 30-October 2, 2022; Chicago, IL.

59

59

Benefit Across Subgroups Is Consistent Among the Pivotal GATHER1 and GATHER2 Studies

12 Month	ACP 2 mg		Sham		FAVORS SHAM / FAVORS ACP
Subgroup	n	LS Mean	n	LS Mean	Difference (CI)
Baseline GA <4 disc area	48	0.33	70	0.43	0.106 (0.007, 0.205)
Baseline GA ≥4 disc area	11	0.29	29	0.43	0.145 (0.023, 0.266)
Baseline VA <50 Letters	1	NE	4	NE	NE
Baseline VA ≥50 Letters	58	0.27	95	0.37	0.107 (0.025, 0.188)
FAF pattern: None/Focal		NE	1	NE	NE
FAF pattern: Banded/Diffuse	54	0.37	87	0.47	0.103 (0.022, 0.184)
Part 1	22	0.33	20	0.42	0.093 (-0.023, 0.209)
Part 2	37	0.31	79	0.42	0.114 (0.012, 0.216)
Overall	59	0.29	99	0.40	0.110 (0.030, 0.190)

-0.3 -0.2 -0.1 0.0 0.1 0.2 0.3
LS Mean Difference (95% CI)

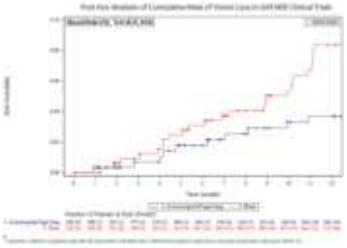
Khanani A, et al. Presented at: AAO 2022. September 30-October 2, 2022; Chicago, IL.

60

60

Functional endpoints for Avacincaptad Pegol

44% reduction (Hazard Ratio 0.56 with 95% CI, 0.15-2.06) and a 59% percent reduction (Hazard Ratio 0.41 with 95% CI, 0.17-1.00) respectively in the rate of vision loss with ACP 2 mg compared to sham over the first 12 months of treatment



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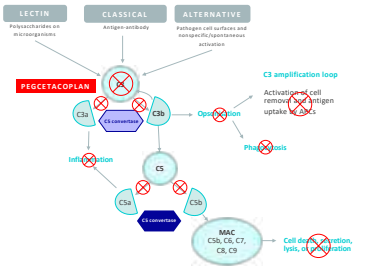
Pegcetacoplan

- All 3 complement pathways involve cleavage of C3
- Inhibition of C3 blocks steps in the complement cascade needed for opsonization, inflammation, and formation of MAC



Liao DS, et al. Ophthalmology. 2020;127(2):186-195.
Ricklin D, et al. Immunol Rev. 2016;274(1):33-58.

62

62

Global Phase 3 Program

DESIGN OF STUDIES (OAKS & DERBY)

Double masked

Randomized 2:2:1:1

- Pegcetacoplan 15 mg/0.1 mL monthly
- Pegcetacoplan 15 mg/0.1 mL EOM
- Sham monthly
- Sham EOM

PRIMARY ENDPOINT AT 12 MONTHS
Change in total area of GA lesions based on fundus autofluorescence

END OF STUDY AT 24 MONTHS
- BCVA, LL-BCVA, low-luminance deficit
- Reading speed
- NEI VFQ-25
- FRI Index composite score
- Microperimetry (OAKS only) – Macular Integrity Assessment (MAIA) device

GALE EXTENSION STUDY (3 YEARS)

Primary Analysis: MMRM Methodology

Fixed Effects:
- Treatment (Sham monthly and EOM were pooled for analysis), time, treatment x time interaction
- Baseline GA lesion and fellow eye CNV >=area strata
- Baseline GA lesion strata × time interaction

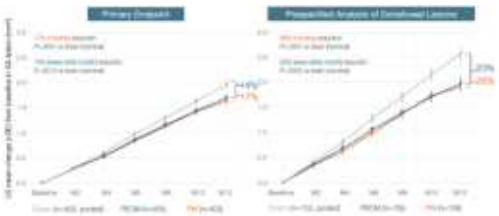
BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; EOM = every other month; FRI = functional reading index; LL = low luminance; MMRM = mixed-effect model for repeated measures; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25.
ClinicalTrials.gov. Updated August 30, 2022. Accessed October 15, 2022. https://clinicaltrials.gov/ct2/show/NCT04770545

63

63

OAKS and DERBY

PEGCETACOPLAN REDUCED LESION GROWTH IN PRESPECIFIED COMBINED ANALYSES OF THE PRIMARY ENDPOINT AND IN EXTRAFOVEAL LESIONS



LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
Heier J, et al. Presented at: The 54th Retina Society 2021. Efficacy of intravitreal pegcetacoplan in geographic atrophy: results from the DERBY and OAKS trials. September 29–October 2, 2021. Chicago, IL.

64

64

Pegcetacoplan Safety Data[a]

Exudations[b]	At 18 Months	At 12 Months
Monthly	39 patients (9.5%)	25 patients (6.0%)
EOM	26 patients (6.2%)	17 patients (4.1%)
Sham	12 patients (2.9%)	10 patients (2.4%)

Infectious Endophthalmitis	At 18 Months	At 12 Months
Monthly	2 cases confirmed	2 cases confirmed
EOM	2 cases confirmed	1 case suspected
Sham	9145 total injections (0.044%)	6331 total injections (0.047%)

Intraocular Inflammation	
At 18 Months	At 12 Months
21 cases (0.23% per injection)	13 cases (0.21% per injection)
No events of retinal vasculitis or retinal vein occlusion	

Pegcetacoplan continues to demonstrate a favorable safety profile at 18 months

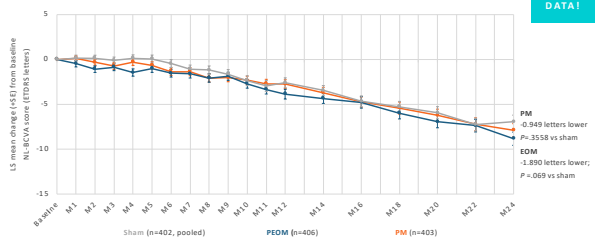
[a] All data are from DERBY and OAKS combined.
[b] Exudations include adverse events reported by the investigator as CNV or neovascular AMD
Goldberg R. Presented at: ARVO 2022; May 1-5, 2022; Denver, CO.
Heier J, et al. Presented at: AAO 2021; November 12-15, 2021; New Orleans, LA.

65

65

OAKS and DERBY Combined BCVA in the Study Eye Over 24 Months

NEW DATA!



LS means estimated from a MMRM. The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye.
Wycoff C, et al. Presented at: AAO 2022. September 30-October 3, 2022; Chicago, IL.

66

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New-Onset nAMD in Study Eye Over 24 Months[a]

OAKS AND DERBY COMBINED

	PM (N=419)	PEOM (N=420)[b]	Sham Pooled (N=417)
New-onset investigator-determined nAMD in study eye, n (%)	**51 (12.2%)**	**28 (6.7%)**	**13 (3.1%)**
Confirmed by reading center, N (%) At time of investigator-reported nAMD, 100% of patients had available SD-OCT and 82% had available FA for reading center evaluation	**37 (8.8%)**	**23 (5.5%)**	**11 (2.6%)**
Reading center-determined CNV cases on protocol-specified FA, not reported as AEs by investigators, n (%)	9 (2.1%)	4 (1.0%)	8 (1.9%)

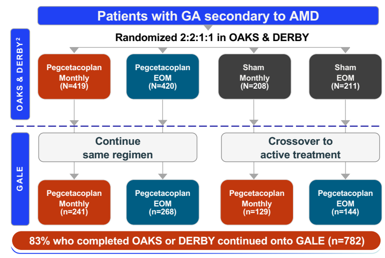
- All investigator-reported AEs are reported as new-onset nAMD in study eye regardless of reading center confirmation
- Patients who developed nAMD continued treatment with study drug and received on-label anti-VEGF therapy at the discretion of the investigator

[a] Events include preferred terms of CNV and neovascular AMD (nAMD). [b] Number of patients at risk for new-onset nAMD in PEOM arms from OAKS and DERBY combined was 419. All data are from safety set. AE = adverse event; FA = fluorescein angiography; VEGF = vascular endothelial growth factor.
Singh R, et al. Presented at: AAO 2022. September 30-October 3, 2022; Chicago, IL. Wycoff C, et al. Presented at: AAO 2022. September 30-October 3, 2022; Chicago, IL.

67

67

GALE: Open-Label Extension Study[1]



Efficacy analysis: Change in GA lesion area based on 12-month GALE data

- 36-month continuous pegcetacoplan treatment compared with sham[a]
  - Pegcetacoplan was compared with sham (actual sham [24 months OAKS and DERBY] + projected sham [12 months GALE])
- 12-month pegcetacoplan treatment for sham crossover group
- Fellow eye vs. study eye
- Microperimetry (OAKS only)

Safety data through 36 months

- Exudative AMD, IOI, ION

[a] Projected sham was estimated by calculating the average of the mean rate of change of each 6-month period of sham treatment.
AMD, age-related macular degeneration; **EOM,** every other month; **GA,** geographic atrophy; **IOI,** intraocular inflammation; **ION,** ischemic optic neuropathy.
1. GALE ClinicalTrials.gov identifier: NCT04770545. 2. Heier JS, et al. *Lancet*. 2023; 402: 1434–48.

68

GALE: Patient Disposition

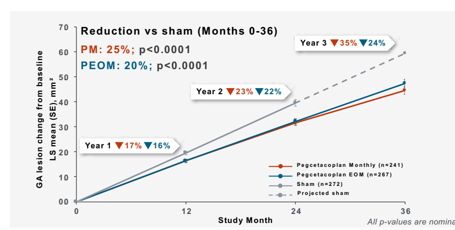
	Number of patients: PM to PM	PEOM to PEOM	SM to PM	SEOM to PEOM	Overall
Enrolled in GALE	250	269	129	144	792
Included in modified full analysis set	241	267	129	143	780
Excluded from modified full analysis set					
No injection received in GALE	0	1	0	1	2
Enrolled from study other than OAKS or DERBY[a]	9	1	0	0	10
Completed GALE through Month 36, n (%)	234 (93.6%)	243 (90.7%)	115 (89.1%)	135 (94.4%)	727 (92.0%)
Discontinued GALE prior to Month 36	16	25	14	8	63
Consent Withdrawal	4	14	6	2	26
Deaths	5	8	5	3	21
Adverse Event	3	3	3	2	11
Lost to Follow-up	4	0	0	0	4
Physician's Decision	0	0	0	1	1

92% Patient Retention in First Year of GALE

[a] Enrolled in GALE from Study 103, included in safety population.
PEOM, pegcetacoplan every other month; **PM,** pegcetacoplan monthly; **SEOM,** sham every other month; **SM,** sham monthly.

69

GALE Total Population (Nonsubfoveal + Subfoveal): Reductions in GA Growth Following 36 Months of Continuous Pegcetacoplan Increased Over Time

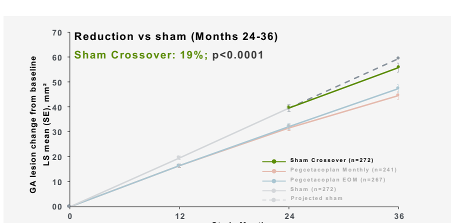


1.49 mm² (PM) & 1.21 mm² (PEOM) of Retinal Tissue Preserved Over 36 Months

LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 36, with knots at Months 12 and 24 allowing for the slope to be linear over each of the 12-month segments but to differ between segments (piecewise slope analysis). Mean rate of change of hypothetical sham from Month 24 to Month 36 was estimated from the mean rate of change in each period from Month 0 to Month 24. The modified full analysis set was used for the analysis, defined as patients who are in OAKS/DERBY antecedent study's ITT set, have not been enrolled in APL2-103, and received ≥1 injection of pegcetacoplan in GALE. Projected sham is shown with a dashed line. Data shown for patients who continued into the GALE trial after OAKS & DERBY.
EOM, every other month; GA, geographic atrophy; ITT, intent to treat; LS, least squares; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly; SE, standard error.

70

GALE Sham Crossover (Nonsubfoveal + Subfoveal): Reductions in GA Growth in First 12 Months of Pegcetacoplan Treatment

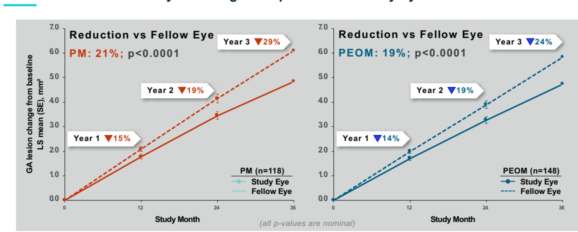


19% Reduction After Crossing over from Sham to Pegcetacoplan for 12 Months

LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 36, with knots at Months 12 and 24 allowing for the slope to be linear over each of the 12-month segments but to differ between segments (piecewise slope analysis). Mean rate of change of hypothetical sham from Month 24 to Month 36 was estimated from the mean rate of change in each period from Month 0 to Month 24. The modified full analysis set was used for the analysis, defined as patients who are in OAKS/DERBY antecedent study's ITT set, have not been enrolled in APL2-103, and received ≥1 injection of pegcetacoplan in GALE. Projected sham is shown with a dashed line. Data shown for patients who continued into the GALE trial after OAKS & DERBY.
EOM, every other month; GA, geographic atrophy; ITT, intent to treat; LS, least squares; PM, pegcetacoplan monthly; SE, standard error.

71

GALE: Untreated Fellow Eyes vs. Pegcetacoplan-Treated Study Eyes Over 36 Months

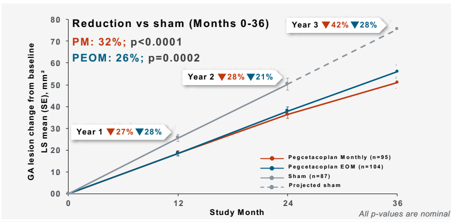


Increasing Effects Over Time in Treated Study Eyes vs. Untreated Fellow Eyes

Study eye vs. fellow eye comparison was prespecified; statistical modeling was performed post hoc. LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 36, with knots at Months 12 and 24 allowing for the slope to be linear over each of the 12-month segments but to differ between segments (piecewise slope analysis). The modified full analysis set was used for the analysis, defined as patients who are in OAKS/DERBY antecedent study's ITT set, have not been enrolled in APL2-103, and received ≥1 injection of pegcetacoplan in GALE. Additionally, patients must have had bilateral GA and a fellow eye with baseline absence of eAMD in the medical history; baseline GA lesion size between 2.5 and 17.5 mm²; presence of any pattern of hyperautofluorescence in the junctional zone of GA; and GA not confluent with any peripapillary atrophy.
eAMD, exudative age-related macular degeneration; GA, geographic atrophy; LS, least squares; mITT, modified intent to treat; PM, pegcetacoplan monthly; PEOM, pegcetacoplan every other month; SE, standard error.

72

GALE Nonsubfoveal Subgroup (n=286 eyes): Reductions in GA Growth with 36 Months of Continuous Pegcetacoplan

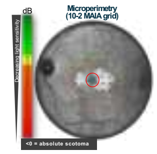


2.44 mm² (PM) & 1.94 mm² (PEOM) of Retinal Tissue Preserved Over 36 Months

LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 36, with knots at Months 12 and 24 allowing for the slope to be linear over each of the 12-month segments but to differ between segments (piecewise slope analysis). Mean rate of change of hypothetical sham from Month 24 to Month 36 was estimated from the mean rate of change in each period from Month 0 to Month 24. The modified full analysis set was used for the analysis, defined as patients who are in OAKS/DERBY antecedent study's ITT set, have not been enrolled in APL2-103, and received ≥1 injection of pegcetacoplan in GALE. Projected sham is shown with a dashed line. Data shown for patients who continued into the GALE trial after OAKS & DERBY.
EOM, every other month; **GA**, geographic atrophy; **ITT**, intent to treat; **LS**, least-squares; **PEOM**, pegcetacoplan every other month; **PM**, pegcetacoplan monthly; **SE**, standard error.

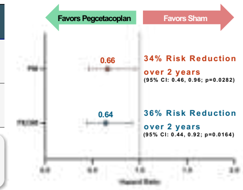
73

Central 4 Macular Loci: Pegcetacoplan Reduces Risk of Progression to Absolute Scotoma (post hoc)



Month 24	Mean (SD) change in BCVA from baseline, ETDRS letters
Patients with complete loss of central 4 loci [n=149]	-11.7 (17.33)
Patients maintaining sensitivity in at least one of central 4 loci [n=183]	-4.9 (11.16)

Occurrence of 4 central scotomatous loci associated with greater loss of vision over 2 years

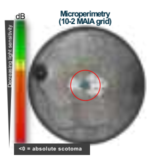


Pegcetacoplan reduces risk of progression to absolute scotoma of central 4 loci

Hazard ratio estimated from Cox Proportional Hazards model including patients in the mITT population at-risk for the event with at least one post-baseline assessment. Model includes Treatment + baseline GA lesion area (< 7.5 mm² or ≥ 7.5 mm²) + baseline presence of choroidal neovascularization in the fellow eye (Yes or No) + baseline number of central 4 scotomatous points.
All p-values are nominal. Microperimetry only performed in OAKS.
CI, confidence interval; **dB**, decibel; **BCVA**, best-corrected visual acuity; **GA**, geographic atrophy; **MAIA**, Macular Integrity Assessment; **mITT**, modified intent to treat; **SD**, standard deviation.

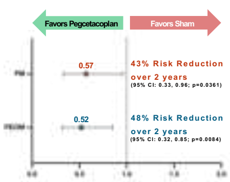
74

Central 16 Macular Loci: Pegcetacoplan Reduces Risk of Progression to Absolute Scotoma (post hoc)



Month 24	Mean (SD) change in BCVA from baseline, ETDRS letters
Patients with complete loss of central 16 loci [n=76]	-12.7 (17.99)
Patients maintaining sensitivity in at least one of central 16 loci [n=316]	-6.3 (13.01)

Occurrence of 16 central scotomatous loci associated with greater loss of vision over 2 years

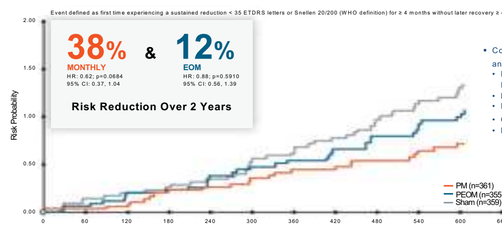


Pegcetacoplan reduces risk of progression to absolute scotoma of central 16 loci

Hazard ratio estimated from Cox Proportional Hazards model including patients in the mITT population at-risk for the event with at least one post-baseline assessment. Model includes Treatment + baseline GA lesion area (< 7.5 mm² or ≥ 7.5 mm²) + baseline presence of choroidal neovascularization in the fellow eye (Yes or No) + baseline number of central 16 scotomatous points.
All p-values are nominal. Microperimetry only performed in OAKS.
CI, confidence interval; **dB**, decibel; **BCVA**, best-corrected visual acuity; **GA**, geographic atrophy; **MAIA**, Macular Integrity Assessment; **mITT**, modified intent to treat; **SD**, standard deviation.

75

Pegcetacoplan Delayed Progression to Persistent Severe Visual Impairment with up to 38% Risk Reduction Over 2 Years



- Consistent with other analyses:
  - Reduced GA growth on FAF, OCT
  - Microperimetry
  - Fellow eye
  - Quartile analysis
  - MAIC

76

GALE: Ocular AEs in the Study Eye over 12 Months

	GALE Integrated Months 24-36			
Adverse events in study eye reported in ≥2% of patients treated with pegcetacoplan in M24-36, %[a]	PM to PM (n=250)	SM to PM (n=129)	PEOM to PEOM (n=268)	SEOM to PEOM (n=143)
Ocular discomfort[a]	3.6%	6.2%	2.6%	7.0%
Exudative age-related macular degeneration[a]	7.9%	5.6%	2.0%	2.9%
Cataract	5.2%	3.9%	1.9%	3.5%
Vitreous floaters	4.4%	10.1%	2.2%	5.6%
Conjunctival hemorrhage	3.2%	9.3%	2.6%	4.2%
Retinal hemorrhage	3.2%	2.3%	2.2%	1.4%
Intraocular pressure increased	4.8%	3.9%	5.2%	1.4%

Safety Profile in First 12 Months of GALE Consistent with OAKS & DERBY

[a]Safety population, consisting of all enrolled patients who received at least 1 pegcetacoplan or sham injection and analyzed according to the actual treatment received. The following terms were combined: Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye. Exudative age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization.
AE, adverse event; **PEOM**, pegcetacoplan every other month; **PM**, pegcetacoplan monthly; **SEOM**, sham every other month; **SM**, sham monthly.

77

GALE: Events of Interest

	GALE Integrated Months 24-36			
Adverse events in study eye, patient (%)	PM to PM (n=250)	SM to PM (n=129)	PEOM to PEOM (n=268)	SEOM to PEOM (n=143)
Infectious endophthalmitis	0	1 (0.8%)	0	0
Intraocular inflammation[a]	6 (2.4%)	5 (3.9%)	2 (0.7%)	2 (1.4%)
Ischemic optic neuropathy	1 (0.4%)	0	0	0
Exudative age-related macular degeneration[b]	PM Total (n=379)		PEOM Total (n=411)	
	7.1%		2.3%	

- Rates from OAKS, DERBY & GALE Months 0-36:
  - Infectious endophthalmitis: ~1/3600 injections [0.03% per injection]
  - ION: ~1/2000 injections [0.05% per injection]
  - IOI[a]: 0.26% per injection
- No study events of occlusive or non-occlusive retinitis or vasculitis
  - Rare events have been reported in the real-world setting at an estimated rate of ~0.01% per injection[1]

>18,000 pegcetacoplan injections across >1100 patients in OAKS, DERBY & GALE 12M; >24,000 injections to date in clinical program

[a]Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare. Excludes 4 cases from 2018 that were due to impurities; the rate is 0.28% per injection including these cases. [b]Exudative age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization.
IOI, intraocular inflammation; **ION**, ischemic optic neuropathy; **PEOM**, pegcetacoplan every other month; **PM**, pegcetacoplan monthly; **SEOM**, sham every other month; **SM**, sham monthly.
1. Apellis Pharmaceuticals, Inc. Press release: "Apellis Announces Preliminary U.S. Net Revenues of Approximately $74 Million for SYFOVRE® (pegcetacoplan injection) in the Third Quarter of 2023." October 5, 2023. Available at: https://investors.apellis.com/news-releases/news-release-details/apellis-announces-preliminary-us-net-revenues-approximately-74. Accessed October 5, 2023.

78

Deciding between FDA approved agents for Geographic Atrophy

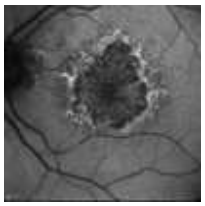
- **Pegcetacoplan**
  - **Longer time for FDA approval**
  - **Flexible dosing every 2 months**
  - **Functional and anatomic endpoints at 2 years**
  - **Recent IOI signs are less and predictable (first or second injection)**
- **Avacincaptad Pegol**
  - **Dosing every 1 month (Year 2 dosing showed benefit)**
  - **Functional endpoints at year 1 not replicated in year 2**
  - **No IOI reported to date**

79

79

Other Approaches

- HtrA1
- Modulate choroidal blood flow
- Antioxidants (eg, metformin)
- Statins
- Tetracyclines
- Optogenetics
- Electrical stimulation



HtrA1 = high-temperature requirement A serine peptidase 1.

80

80

Summary of Current and Future Treatment Landscape

- Most drugs in development are designed for intravitreal administration
- Several therapeutic avenues to reduce the rate of disease progression are being investigated, such as:
  - Drugs with antioxidative properties
  - Inhibitors of the complement cascade
  - Visual cycle inhibitors
  - Regulators of MAC formation
  - Gene therapy

81

81

Thank you!

Questions?

82

82