Safety of intravitreal pegcetacoplan in geographic atrophy: results from the DERBY and OAKS trials

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Disclosures

- Dr. Wykoff has the following Disclosures:
  - Consulting: AbbVie, Adverum, Aerie Pharmaceuticals, Allergan, Allgenesis, Alnylam, Annexon, Apellis, Arrowhead Pharmaceuticals, Bausch + Lomb, Bayer, Bionic Vision Technologies, Chengdu Kanghong Biotechnologies (KHB), Clearside Biomedical, EyePoint Pharmaceuticals, Genentech, Gyroscope, IVERIC Bio, Janssen, Kato Pharmaceuticals, Kodiak Sciences, Long Bridge Medical, NGM Biopharmaceuticals, Novartis, OccuRx, Ocular Therapeutix, ONL Therapeutics, Opthea Limited, Palatin, Perfuse Therapeutics, PolyPhotonix, RecensMedical, Regeneron, RegenXBio, Roche, Surrozen, Takeda, Valo, Verana Health, Vitranu
  - Research: Adverum, Aerie Pharmaceuticals, Aldeyra, Alimera Sciences, Alkahest, Allergan, Amgen, Annexon, Apellis, Asclepix, Bayer, Boehringer Ingelheim, Chengdu Kanghong Biotechnology, Clearside Biomedical, Gemini, Genentech, Graybug Vision, Gyroscope, IONIS Pharmaceutical, iRENIX, IVERIC bio, Kodiak Sciences, LMRI, Nanoscope, Neurotech Pharmaceuticals, NGM Biopharmaceuticals, Novartis, Ocular Therapeutix, Opthea, Oxurion, RecensMedical, Regeneron, RegenXBio, Roche, SamChunDang Pharm, Taiwan Liposome Company, Xbrane BioPharma
  - Ownership/Stock: ONL Therapeutics, PolyPhotonix, RecensMedical, Visgenx

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Outline

- Patient Disposition and Drug Exposure
- Overall AEs and SAEs
- Cases of Intraocular Inflammation
- Cases of Infectious Endophthalmitis
- Cases of Exudative AMD

AMD=age-related macular degeneration; AE=adverse event; SAE=serious AE.

Patient Disposition

Patient disposition

	OAKS			DERBY		
	PM (N=213)	**PEOM (N=212)**	**Sham Pooled (N=212)**	**PM (N=206)**	**PEOM (N=208)**	**Sham Pooled (N=207)**
Completed study through Month 12, n (%)	184 (86.4%)	190 (89.6%)	191 (90.1%)	183 (88.8%)	188 (90.4%)	179 (86.5%)
Discontinued study prior to Month 12, n (%)	29 (13.6%)	22 (10.4%)	21 (9.9%)	23 (11.2%)	20 (9.6%)	28 (13.5%)
Reason for discontinuation						
Consent withdrawal	14 (6.6%)	11 (5.2%)	9 (4.2%)	15 (7.3%)	10 (4.8%)	15 (7.2%)
Death	7 (3.3%)	3 (1.4%)	4 (1.9%)	5 (2.4%)	0	3 (1.4%)
Adverse event	3 (1.4%)	5 (2.4%)	2 (0.9%)	1 (0.5%)	4 (1.9%)	5 (2.4%)
COVID-19 impact	3 (1.4%)	2 (0.9%)	5 (2.4%)	1 (0.5%)	6 (2.9%)	5 (2.4%)
Lost to follow-up	2 (0.9%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0

N=number of patients; PM=pegcetacoplan monthly; PEOM=pegcetacoplan every other month.

Exposure

	OAKS			DERBY		
	PM (N=202)	PEOM (N=205)	Sham Pooled (N=206)	PM (n=201)	PEOM (n=200)	Sham Pooled (n=194)
Total number of injections received	2056	1103	1597	2058	1063	1496
Total number of missed injections, n (%)	252 (9.2%)	86 (7.2%)	203 (11.3%)	281 (12.0%)	109 (9.3%)	184 (11.0%)
Mean number of injections/patient, n, % (SD)	10.2/12, 85% (2.31)	5.4/6, 90% (1.2)	7.8/9, 87% (3.08)	10.2/12, 85% (2.24)	5.3/6, 88% (1.05)	7.7/9, 86% (3.02)
Mean duration[a] of treatment, days (SD)	334.5 (65.40)	337.8 (63.21)	332.3 (64.05)	335.3 (60.98)	338.0 (56.52)	335.6 (60.09)

Approximately half of missed injections were attributed to COVID-19

[a]Duration of treatment in monthly group is (date of last injection + 30 days) – date of first injection + 1; EOM group is (date of last injection + 60 days) – date of first injection + 1. Duration of treatment is truncated to a patient's early termination date, Month 12 cutoff date, or study completion date, as appropriate.
EOM=every other month; N=number; PM=pegcetacoplan monthly; PEOM=pegcetacoplan EOM; SD=standard deviation.

Overall AEs and SAEs

Overall TEAEs

Note: Sham patients do not receive injections

	OAKS		
	PM (N=213)	PEOM (N=212)	Sham pooled (N=211)
All TEAEs, n (%)	170 (79.8%)	160 (75.5%)	154 (73.0%)
Total events, M	751	721	666
Ocular TEAEs in study eye			
Patients, n (%)	108 (50.7%)	97 (45.8%)	74 (35.1%)
Total events, M	256	208	159
Non-ocular TEAEs			
Patients, n (%)	136 (63.8%)	127 (59.9%)	125 (59.2%)
Total events, M	390	412	413
Serious ocular TEAEs in the study eye, n (%) M	3 (1.4%) 3	4 (1.9%) 4	0
Optic ischaemic neuropathy	1 (0.5%) 1	0	0
Papilloedema	1 (0.5%) 1	0	0
Retinal detachment	0	1 (0.5%) 1	0
Endophthalmitis[a]	1 (0.5%) 1	3 (1.4%) 3	0

[a]The events of endophthalmitis include infectious and non-infectious endophthalmitis
Any adverse events with missing or unknown severity were considered as severe. Note that n indicates the number of patients. M indicates number of events.
AE=adverse event; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; TEAEs=treatment-emergent AE.

Overall TEAEs

Note: Sham patients do not receive injections

	DERBY		
	PM (N=206)	**PEOM (N=208)**	**Sham pooled (N=206)**
All TEAEs, n (%)	158 (76.7%)	155 (74.5%)	145 (70.4%)
Total events, M	708	600	530
Ocular TEAEs in study eye			
Patients, n (%)	100 (48.5%)	91 (43.8%)	72 (35.0%)
Total events, M	227	162	126
Non-ocular TEAEs			
Patients, n (%)	127 (61.7%)	110 (52.9%)	112 (54.4%)
Total events, M	396	339	329
Serious ocular TEAEs in the study eye, n (%) M	1 (0.5%) 1	0	2 (1.0%) 2
Vitritis	1 (0.5%) 1	0	0
Dry AMD	0	0	1 (0.5%) 1
Macular hole	0	0	1 (0.5%) 1

Any adverse events with missing or unknown severity were considered as severe.
AMD=age-related macular degeneration; M=number of events; n=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; TEAEs=treatment-emergent adverse event.

Most common ocular AEs in the study eye (≥5%)

OAKS

	PM (N=213)	PEOM (N=212)	Sham pooled (N=211)
Number of patients with ≥1 ocular TEAE in the study eye, n (%) M	108 (50.7%) 256	97 (45.8) 208	74 (35.1) 159
Ocular TEAEs in study eye in ≥5% of pegcetacoplan patients, n (%) M			
Conjunctival hemorrhage	18 (8.5%) 30	13 (6.1%) 16	6 (2.8%) 6
Eye pain	15 (7.0%) 17	12 (5.7%) 14	11 (5.2%) 14
Vitreous floaters	9 (4.2%) 10	15 (7.1%) 20	1 (0.5%) 1

DERBY

	PM (N=206)	PEOM (N=208)	Sham pooled (N=206)
Number of patients with ≥1 ocular TEAE in the study eye, n (%) M	100 (48.5%) 227	91 (43.8) 162	72 (35.0%) 126
Ocular TEAEs in study eye in ≥5% of pegcetacoplan patients, n (%) M			
Vitreous floaters	18 (8.7%) 22	4 (1.9%) 5	3 (1.5%) 3

AEs that occurred in at least 5% of pooled pegcetacoplan patients are listed by preferred term (PT).
AE=adverse event; AMD, age-related macular degeneration; M=number of events; n=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; TEAEs=treatment-emergent AE.

Cases of IOI

Intraocular inflammation (IOI): OAKS & DERBY historical context

- 2018: Following 4 cases of intraocular inflammation, DERBY and OAKS were temporarily put on hold
  - Cases of inflammation were found to be due to an impurity in the IP
- Impurity was removed
- 2019: Trials were resumed

IOI=intraocular inflammation; IP, investigational product

Intraocular inflammation (IOI)

	OAKS & DERBY combined		
	PM (N=419)	PEOM (N=420)	Sham Pooled (N=417)
Patients with ≥1 event of IOI	9 (2.1%)	4 (1.0%)	0
Cases of IOI			
Vitritis	5 (1.1%)	0	0
Iridocyclitis	2 (0.4%)	2 (0.4%)	0
Iritis	2 (0.4%)	0	0
Anterior chamber cell	1 (0.2%)	0	0
Anterior chamber flare	0	1 (0.2%)	0
Noninfectious endophthalmitis	0	1 (0.2%)	0

- There were no cases of vasculitis or occlusive vasculitis
- Four cases, including noninfectious (culture negative) endophthalmitis, were reported in 2018 and linked to drug impurity
- Percentage of patients experiencing IOI:
  - receiving pegcetacoplan: 1.5%
  - receiving pegcetacoplan excluding 2018 cases linked to drug impurity: 1.1%
- **Majority of cases were mild, and 10/13 patients resumed IP administration, without subsequent recurrence of IOI**

IOI=intraocular inflammation; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

Cases of Infectious Endophthalmitis

Infectious endophthalmitis

	OAKS & DERBY combined		
	PM (N=419)	**PEOM (N=420)**	**Sham Pooled (N=417)**
Patients with ≥1 event of infectious endophthalmitis, n (%)	1 (0.2%)	2 (0.5%)	0

- Two cases with culture positive for Gram+; one case with no culture results
- All patients treated with IVT antibiotics; one case treated also with PPV
- Favorable visual acuity outcomes for all patients
- Rate of infectious endophthalmitis per injection: 0.047%
- Rate of infectious endophthalmitis per patient over 12 months: 0.36%

IVT=intravitreal; PEOM= pegcetacoplan every other month; PM= pegcetacoplan monthly; PPV=pars plana vitrectomy.

Cases of Exudative AMD

Non-exudative nAMD

Natural History of Subclinical Neovascularization in Nonexudative Age-Related Macular Degeneration Using Swept-Source OCT Angiography

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

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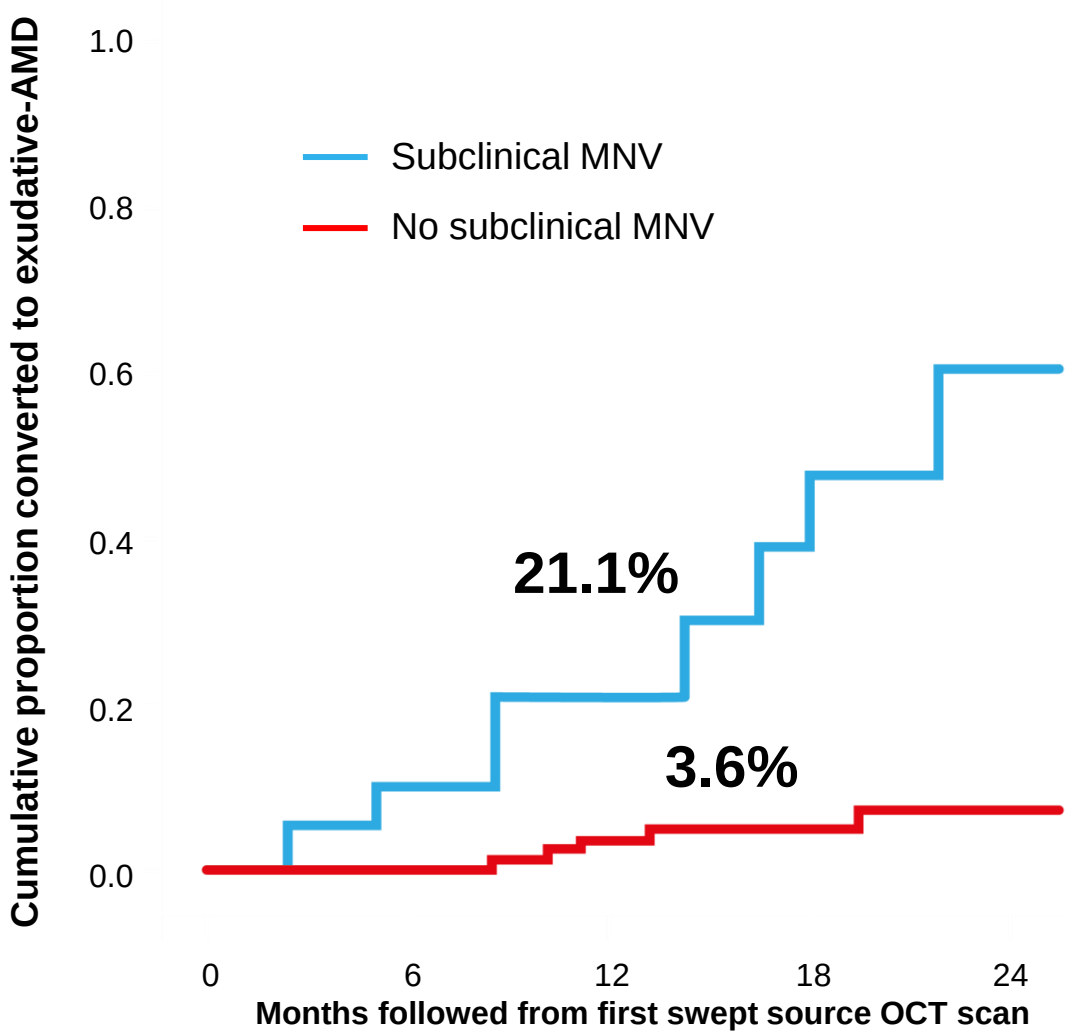
2018

160 eyes with intermediate dry AMD or GA

- 14.4% = subclinical MNV = non-exudative nAMD

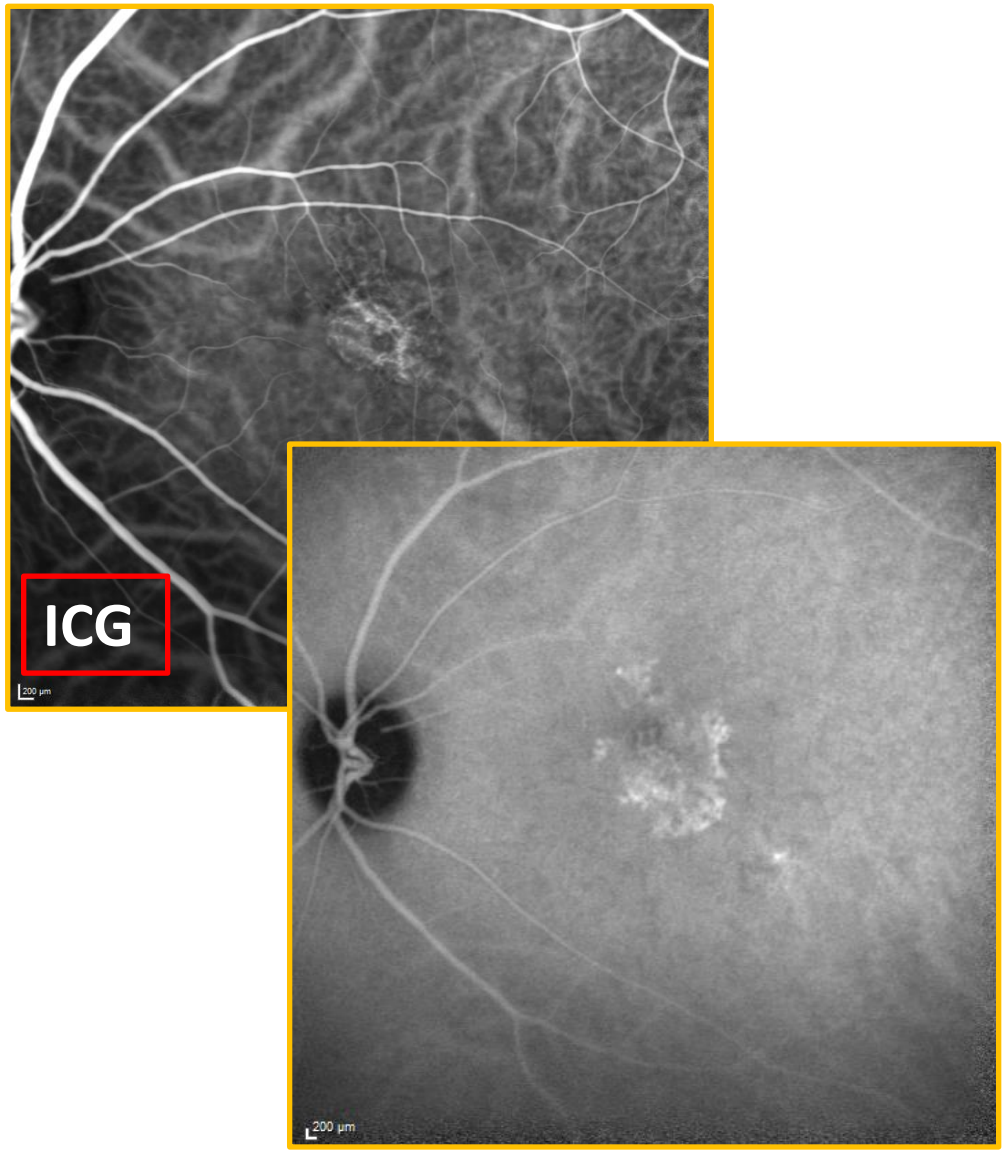
Conversion to exudative AMD

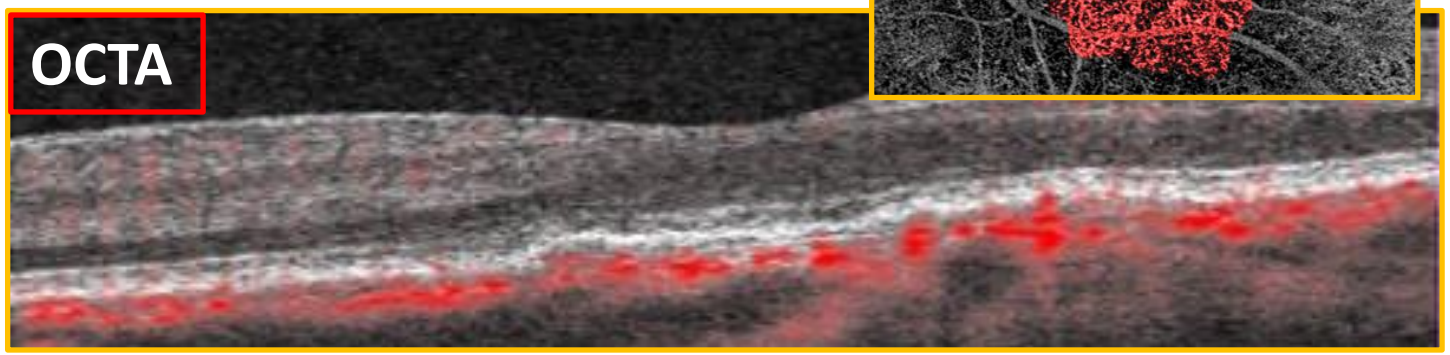
- Subclinical MNV = 15.2× increased risk of exudation

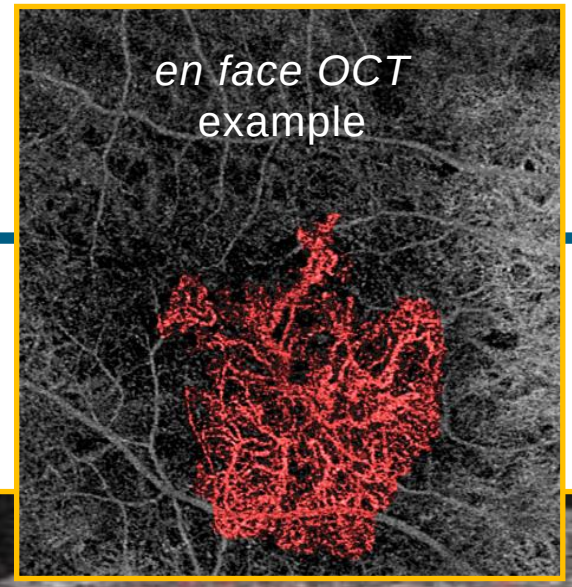


AMD=age-related macular degeneration; GA=geographic atrophy; MNV=macular neovascularization; nAMD=neovascular age-related macular degeneration; OCT=optical coherence tomography.
de Oliveira Dias JR et al. Ophthalmology 2018;125:255–66.

Non-exudative nAMD



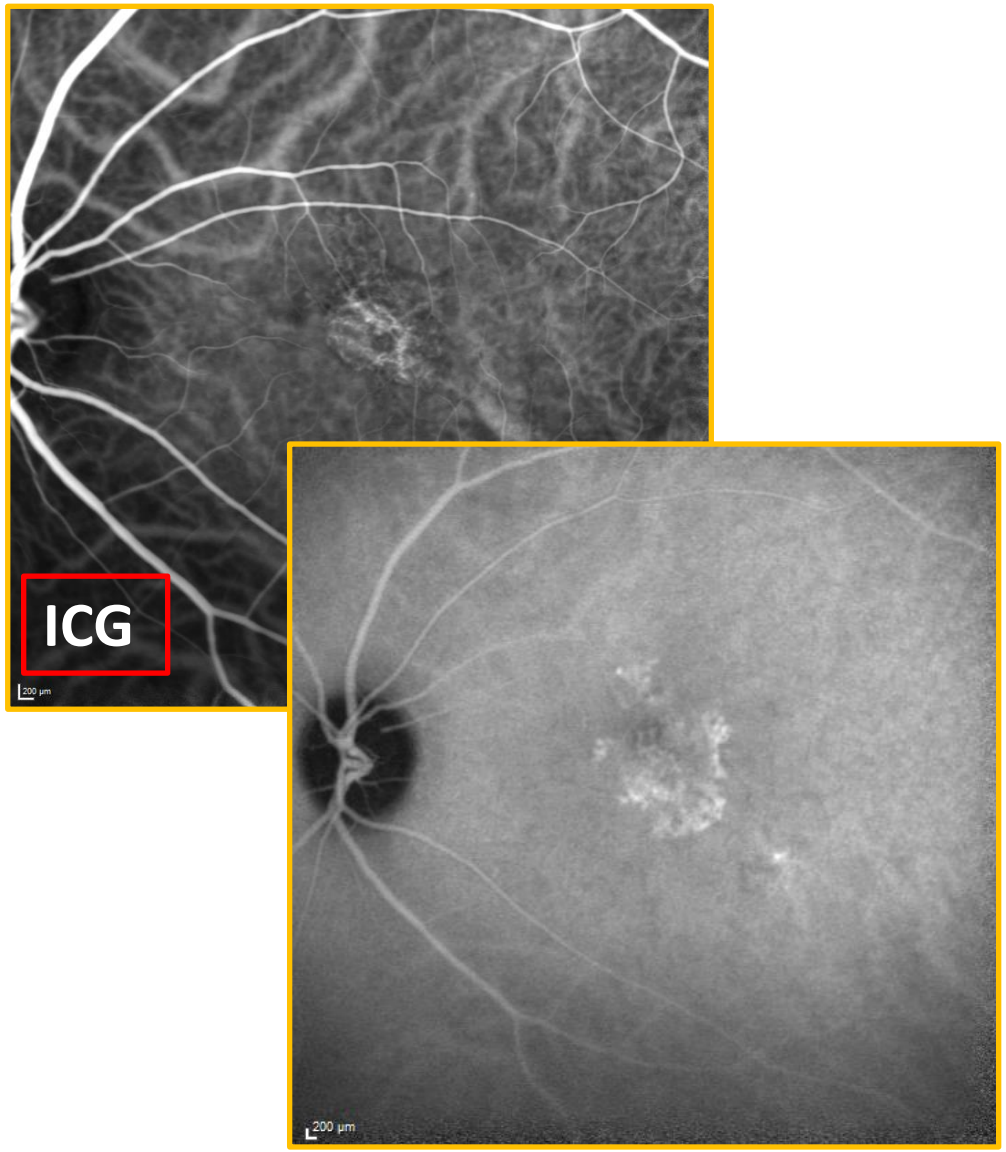


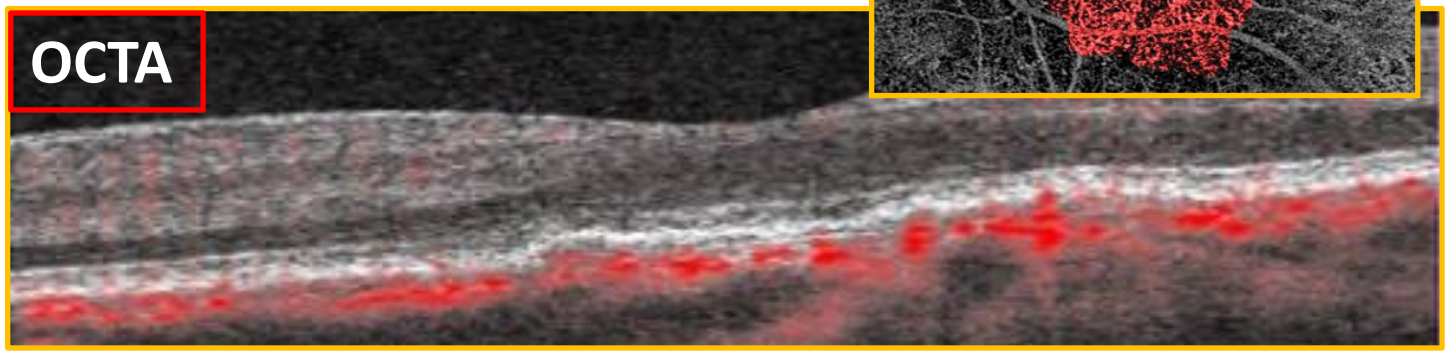


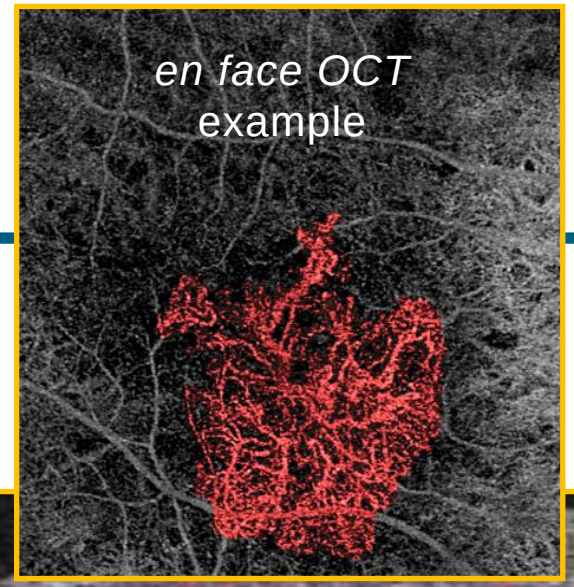
Most prospective GA studies are limited in that they do not routinely include OCTA or ICG in all patients

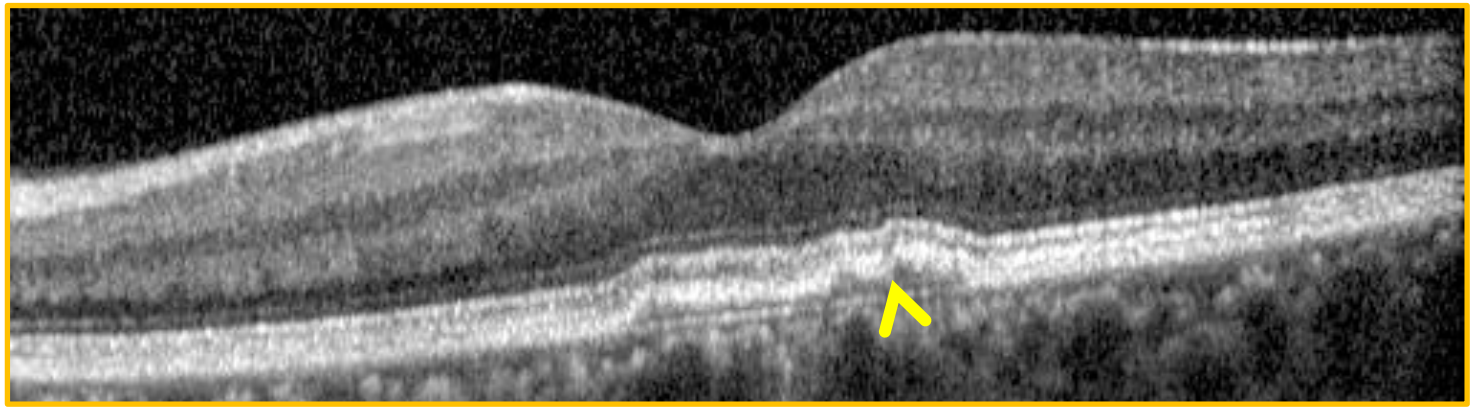
en face OCT is a separate case courtesy of Frank Holtz.
ICG=indocyanine green; GA=geographic atrophy; nAMD=neovascular age-related macular degeneration; OCT=optical coherence tomography; OCTA=OCT angiography.
Wykoff CC et al. Ophthalmology 2021;128:1325–36.

Non-exudative nAMD









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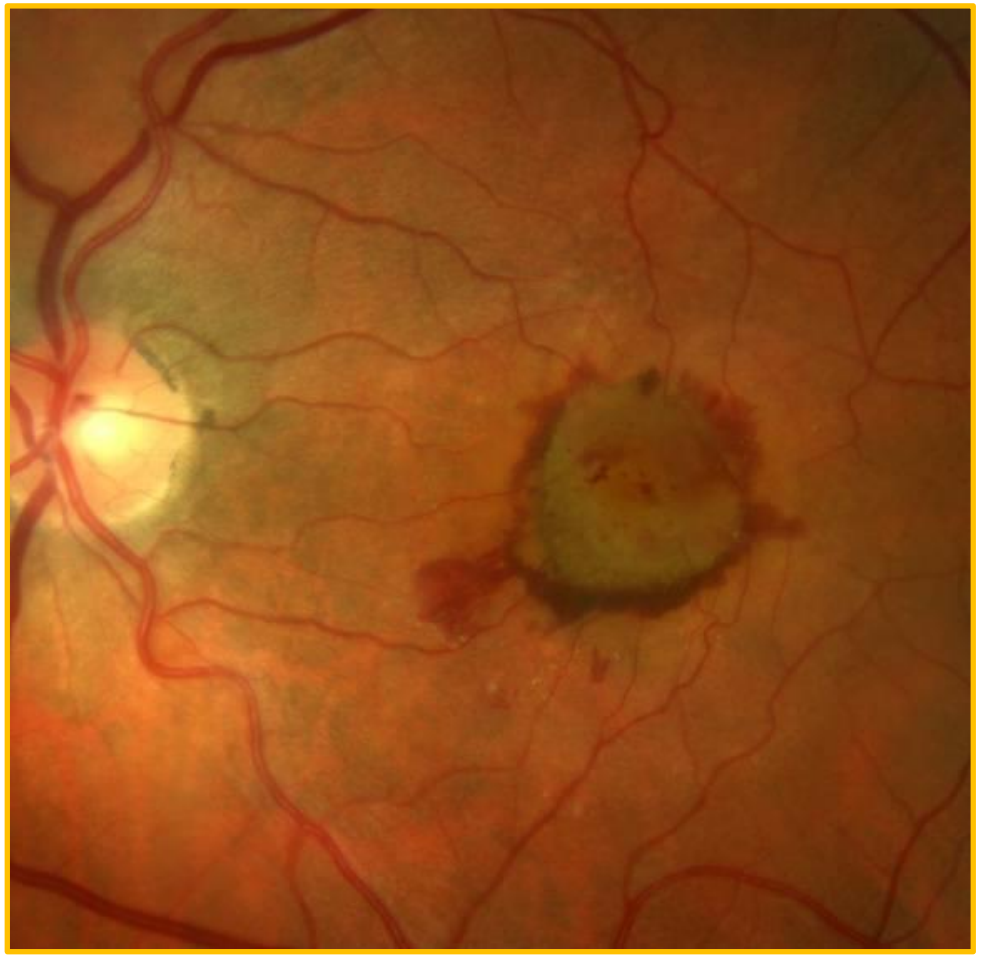
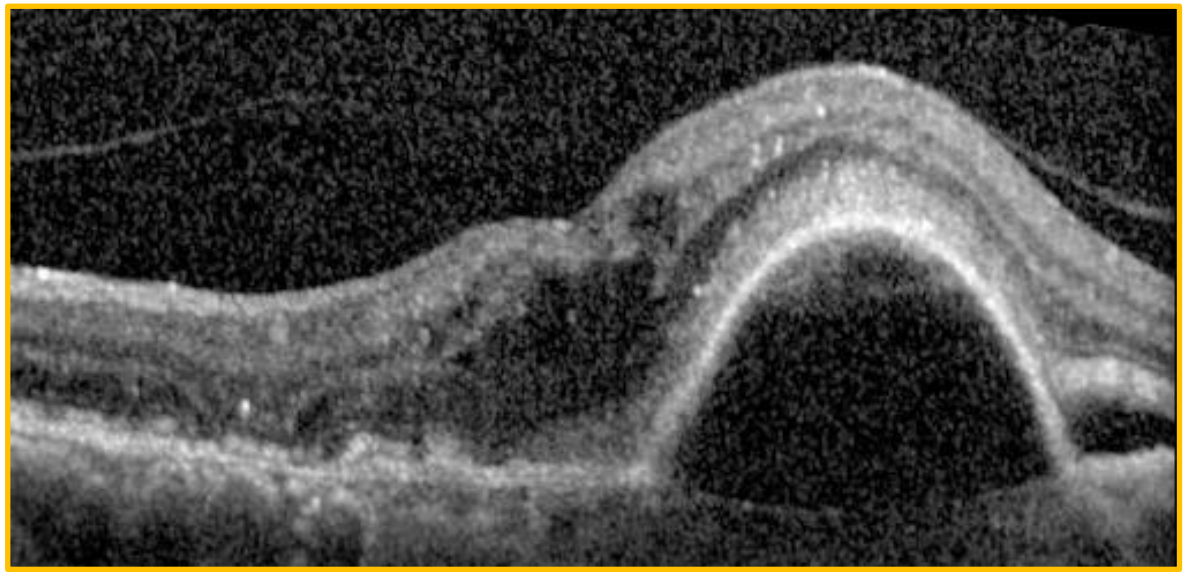
Double-Layer Sign

Exudative AMD





Images courtesy of Charles Wykoff.
AMD=age-related macular degeneration.

Phase 2 FILLY trial: New onset study eye eAMD

Characterizing New-Onset Exudation in the Randomized Phase 2 FILLY Trial of Complement Inhibitor Pegcetacoplan for Geographic Atrophy

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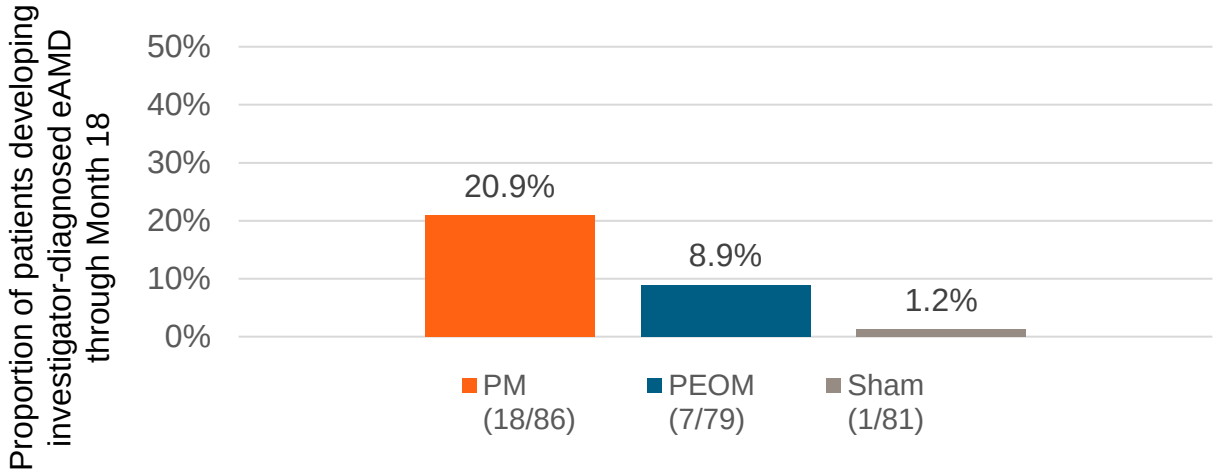
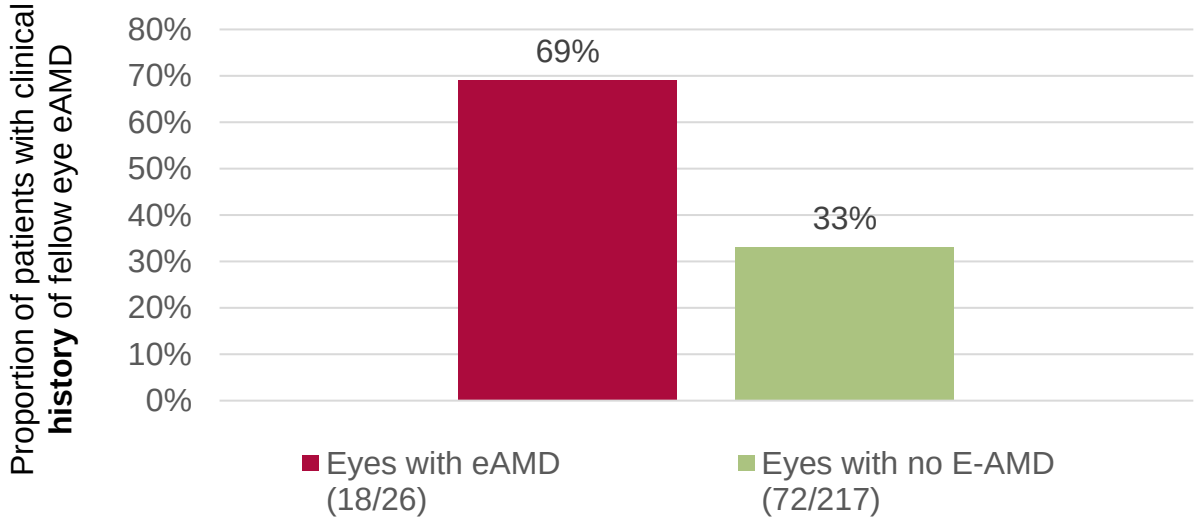
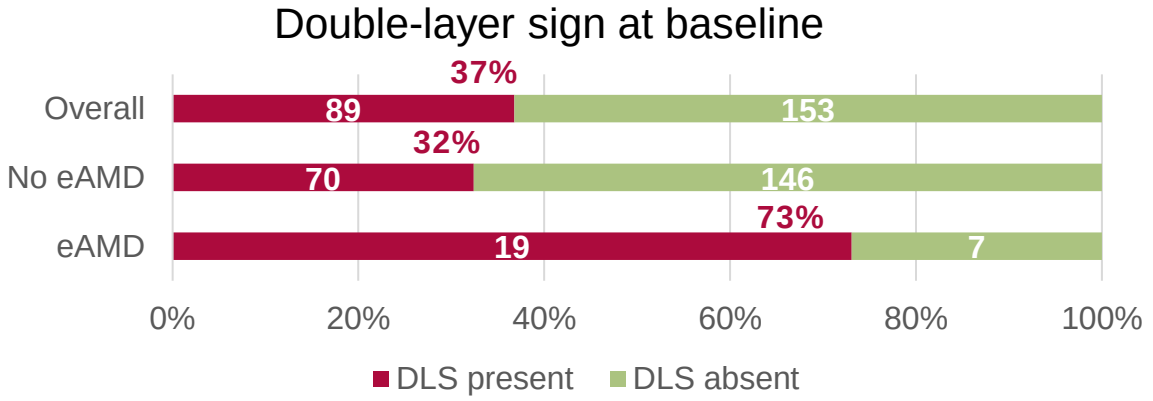




- An unexpected, dose-dependent difference in investigator-determined study eye eAMD
- Associated with greater probability of eAMD development:
  - Fellow eye eAMD
  - DLS on SD-OCT



AMD=age-related macular degeneration; DLS=double-layer sign; eAMD=exudative AMD; PM=pegcetacoplan monthly; PEOM=pegcetacoplan every other month; SD-OCT=spectral domain optical coherence tomography.

Wykoff CC et al. Ophthalmology 2021;128:1325–36.

eAMD findings from FILLY informed the design of the Phase 3 program

OAKS DERBY

- If eAMD suspected, prespecified imaging (CFP, OCT, FA & OCTA [select sites]) captured

- Once MNV verified by masked reading center, patients remain on study treatment and also treated with on-label anti-VEGF pharmacotherapy
  - Initiation of anti-VEGF therapy for eAMD is at the discretion of the investigator and is not reading-center determined

- Within the reporting from OAKS and DERBY
  - Reports of eAMD include all adverse events reported by the investigator falling within the preferred terms neovascular AMD or CNV
  - Cases of MNV detected by the reading center by FA at Month 12, but not reported by investigators as adverse events, were also captured

AMD=age-related macular degeneration; CFP=color fundus photography; CNV=choroidal neovascularization; eAMD=exudative AMD; FA=fundus autofluorescence; MNV=macular neovascularization; OCT=optical coherence tomography; OCTA=OCT angiography; VEGF=vascular endothelial growth factor.

Phase 3 program:
Relevant ocular inclusion and exclusion criteria

- Fellow eye
  - No exclusion criteria related to the fellow eye
  - History of fellow eye eAMD not exclusionary

- Study eye
  - Any history of or evidence of active eAMD was exclusionary
  - Patients with subclinical MNV either by DLS or OCTA were <u>not</u> excluded

DLS=double-layer sign; eAMD=exudative age-related macular degeneration; MNV=macular neovascularization; OCTA=optical coherence tomography angiography.

Characteristics of eAMD in study eye[a]

	OAKS			DERBY		
	PM	PEOM	Sham Pooled	PM	PEOM	Sham Pooled
Patients with investigator-determined new onset eAMD, n (%)	11 (5.2%)	10 (4.7%)	3 (1.4%)	14 (6.8%)	7 (3.4%)	7 (3.4%)
Cases of MNV (FA) detected by reading center but not reported by investigator as AE	2	3	5	0	1	1
Sum of investigator-determined eAMD and reading center cases not reported by investigators	13 (6.1%)	13 (6.1%)	8 (3.8%)	14 (6.8%)	8 (3.8%)	8 (3.9%)

- There were no significant changes in BCVA; findings in OCT were as expected
- Six out of 52 investigator-determined cases were not confirmed by the reading center
- All reading center determined cases that were not reported by investigators as AEs were occult
- All cases with available FA showed occult MNV except for two classical cases in DERBY
- **Combined investigator-determined eAMD rates across the studies: 6.0% PM, 4.1% PEOM, 2.4% Sham**
  - **Including reading center detected cases not reported by investigators: 6.4% PM, 5.0% PEOM, 3.8% Sham**

[a]Events include preferred terms of choroidal neovascularization and neovascular AMD. FA was captured per protocol at Screening and Month 12.
MNV includes Type 1, 2, and 3 neovascularization
AE=adverse event; AMD=age-related macular degeneration; BCVA, best corrected visual acuity; eAMD=exudative AMD; FA=fluorescein angiography; MNV=macular neovascularization; N=number of patients; OCT=optical coherence tomography; PEOM=pegcetacoplan every other month; PM=pegcetacoplan every month; VEGF=vascular endothelial growth factor.

Treatment of eAMD in study eye[a]

	OAKS			DERBY		
	PM	PEOM	Sham Pooled	PM	PEOM	Sham Pooled
Patients with new onset eAMD, n (%)	11 (5.2%)	10 (4.7%)	3 (1.4%)	14 (6.8%)	7 (3.4%)	7 (3.4%)
Patients with concomitant anti-VEGF injections in study eye, n (%)	11 (100%)	10 (100%)	3 (100%)	14 (100%)	6 (85.7%)	5 (71.4%)

- None of the cases detected by the reading center but not reported by investigators were treated with anti-VEGF
- Patients continue to receive study medication according to their randomized arm

[a]Events include preferred terms of choroidal neovascularization and neovascular AMD.
FA was captured per protocol at Screening and Month 12.
AMD=age-related macular degeneration; N=number of patients; FA=fluorescein angiography; PEOM=pegcetacoplan every other month; PM=pegcetacoplan every month; VEGF=vascular endothelial growth factor.

Conclusions

- In the Phase 3 DERBY and OAKS studies, the design and approach were adapted based on learnings from the Phase 2 FILLY study
- Overall, pegcetacoplan administered monthly or every other month was well tolerated in patients with GA
- 1.1% of patients developed IOI; majority of cases were mild, and most patients resumed IP administration
- Rate of endophthalmitis were in line with previous prospective pivotal trials of intravitreal therapeutics
- 6.0%, 4.1%, and 2.4% of patients in the combined PM, PEOM, and sham groups experienced new-onset investigator-determined eAMD
  - Patients who developed eAMD continued treatment with pegcetacoplan and received anti-VEGF therapy per the label

eAMD=exudative age-related macular degeneration; GA=geographic atrophy; IOI=intraocular inflammation; IP=investigational product; PEOM=pegcetacoplan every other month; PM=pegcetacoplan every month; VEGF=vascular endothelial growth factor.