Treatment of Geographic Atrophy Secondary to Age-Related Macular Degeneration With Pegcetacoplan: Updates on the Randomized Phase 3 DERBY and OAKS Trials

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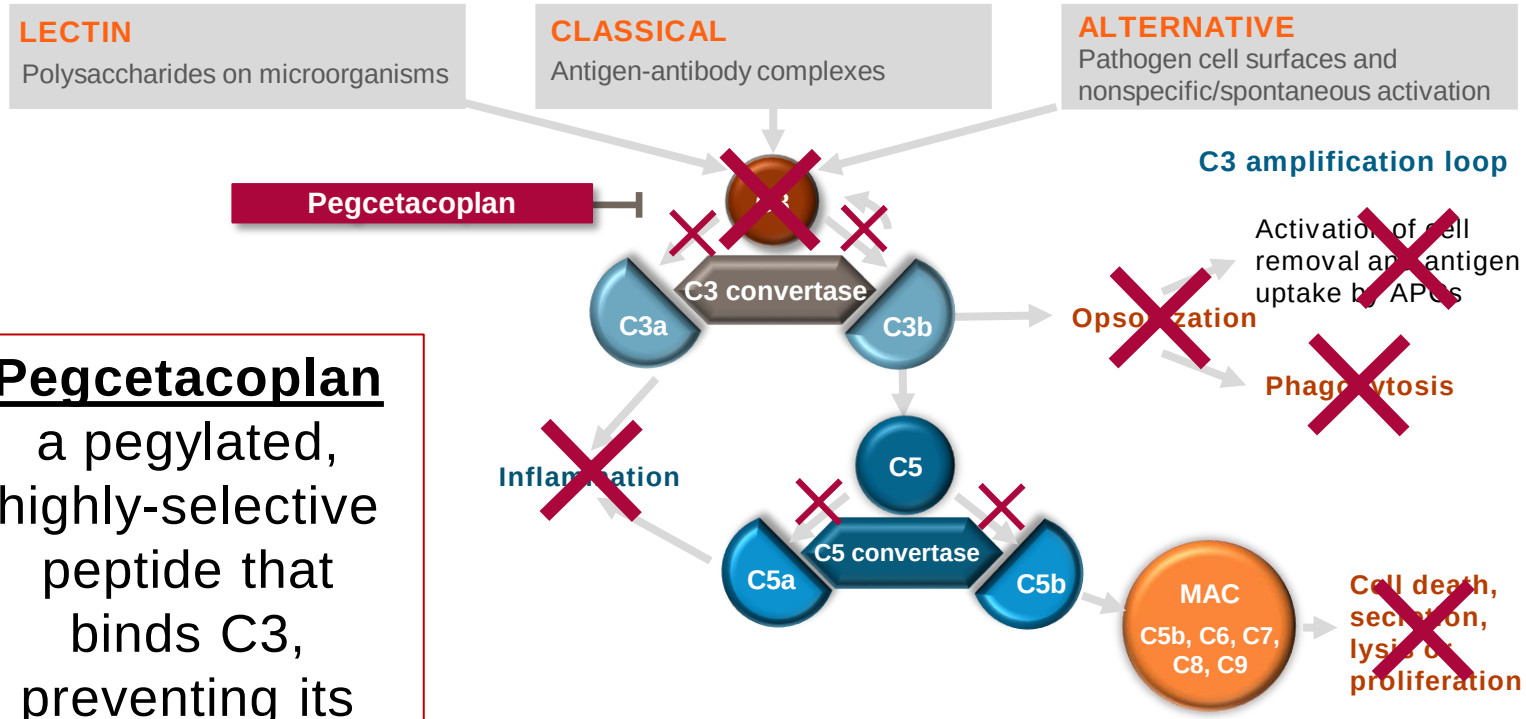
Disclosures

- 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

- Studies funded by Apellis Pharmaceuticals

Introduction



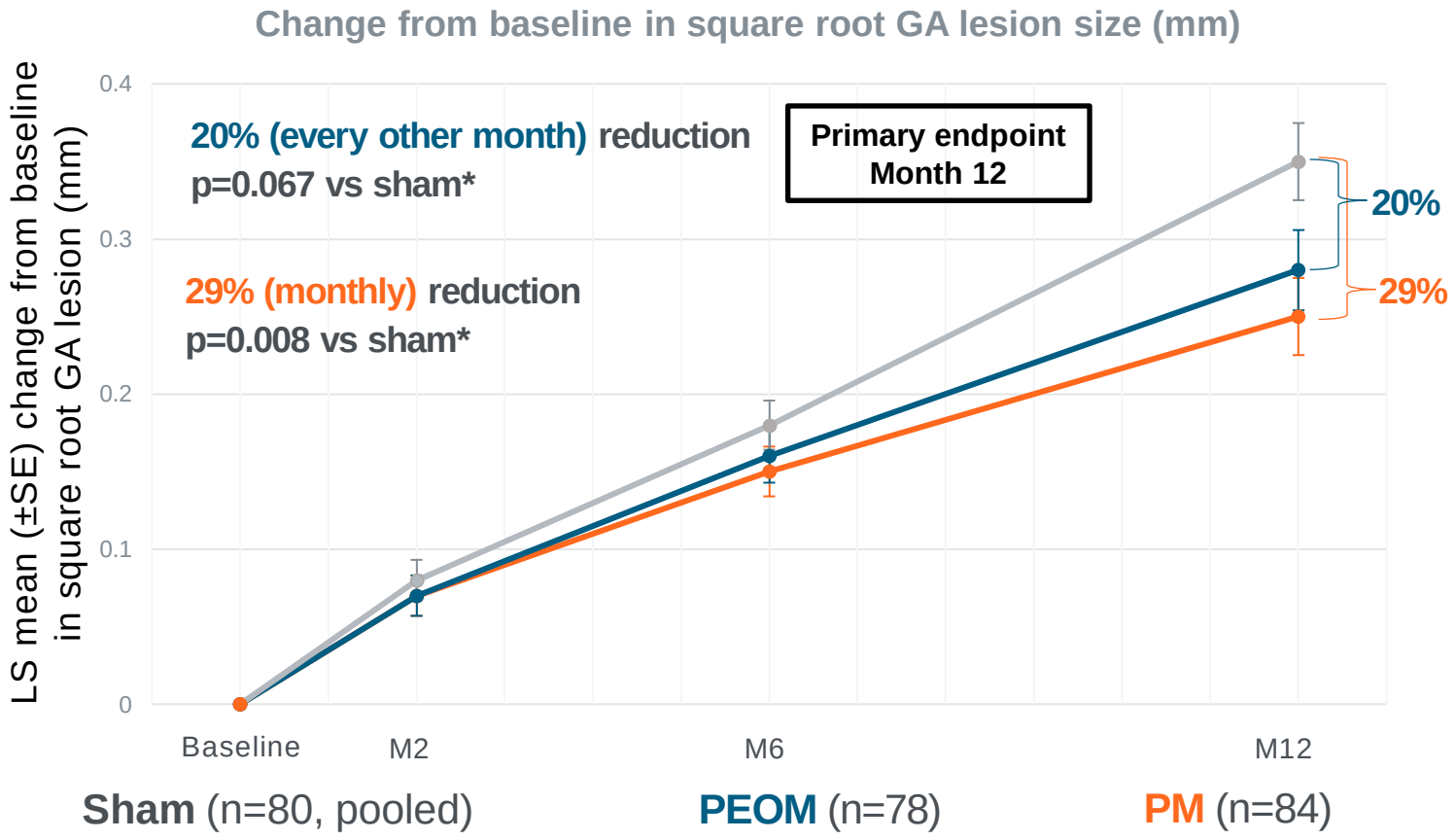
Pegcetacoplan
a pegylated, highly-selective peptide that binds C3, preventing its cleavage

- Dysregulation of the complement cascade has been implicated in GA pathogenesis
- All 3 complement pathways end in the central cleavage of C3
- Inhibition of C3 blocks steps in the complement cascade needed for opsonization, inflammation, and formation of MAC

Figure adapted from Ricklin D, et al. Immunol Rev 2016;274(1):33–58.
APC=antigen-presenting cell; GA=geographic atrophy; MAC=membrane attack complex.
Liao DS, et al. Ophthalmology 2020;127:186–95.

Introduction and objective

Phase 2 FILLY Results



Phase 3 DERBY & OAKS Objective

Assess the efficacy and safety of multiple intravitreal injections of pegcetacoplan in patients with GA secondary to AMD

*P<0.1 was the predefined threshold for statistical significance in FILLY.
AMD=age-related macular degeneration; GA=geographic atrophy; LS=least squares; M=Month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Liao DS, et al. Ophthalmology 2020;127:186–95.

Global phase 3 program: Design of studies (OAKS & DERBY)

OAKS DERBY

Patients with GA secondary to AMD

~600 patients at ~200 sites globally in 2 studies (1258 enrollees total)

APL-2 303 (DERBY)
CT.gov identifier:
NCT03525600

APL-2 304 (OAKS)
CT.gov identifier:
NCT03525613

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

Primary Analysis: MMRM Methodology

Fixed Effects:
- Treatment*, time, treatment x time interaction
- baseline GA lesion and fellow eye CNV area strata
- baseline GA lesion strata × time interaction

**Sham Monthly and EOM were pooled for analysis*

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)

APL-2 305 (GALE)
CT.gov identifier:
NCT04770545

AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CNV=choroidal neovascularization; EOM=every other month; FRI=functional reading index; GA=geographic atrophy; LL=low luminance; MMRM=mixed-effect model for repeated measures; NEI-VFQ=National Eye Institute Visual Function Questionnaire-25.

Key inclusion and exclusion criteria

Key inclusion criteria

- Age ≥60 years
- BCVA ≥24 letters ETDRS (20/320 Snellen equivalent)
- GA lesion requirements:
  - Total size: ≥2.5 and ≤17.5 mm^2
  - Foveal and extrafoveal GA allowed
  - If multifocal, at least 1 focal lesion must be ≥1.25 mm^2 (0.5 DA)
  - Presence of perilesional hyperautofluorescence

Key exclusion criteria

- GA secondary to a condition other than AMD, such as Stargardt disease in either eye
- Ocular history of or active exudative AMD in the study eye, including presence of RPE tear (assessed by reading center)

Ocular history of exudative AMD in the fellow eye is not exclusionary

AMD=age-related macular degeneration; BCVA=best-corrected visual acuity; DA=disc area; ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; RPE=retinal pigment epithelium.

Patient disposition and exposure

	OAKS			DERBY		
Patient disposition[a]	**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%)
Exposure[b]	**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 (10.9%)	86 (7.2%)	203 (11.3%)	281 (12.0%)	109 (9.3%)	184 (11.0%)

Approximately half of missed injections were attributed to COVID-19

[a]Intent-to-treat set.
[b]Modified intent-to-treat set. Patients must have received at least 1 injection and had a baseline and at least one post-baseline value of GA lesion area in the study eye.
COVID=coronavirus disease; GA=geographic atrophy; N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

Key demographics and baseline study eye characteristics

Characteristic		OAKS PM (N=202)	OAKS PEOM (N=205)	OAKS Sham Pooled (N=206)
Age, mean (SD)		78.8 (7.24)	78.1 (7.74)	78.6 (7.26)
Female, n (%)		125 (61.9%)	117 (57.1%)	133 (64.6%)
Male, n (%)		77 (38.1%)	88 (42.9%)	73 (35.4%)
Geographic region				
US, n (%)		147 (72.8%)	142 (69.3%)	147 (71.4%)
ROW, n (%)		55 (27.2%)	63 (30.7%)	59 (28.6%)
Caucasian, n (%)		185 (91.6%)	189 (92.2%)	187 (90.8%)
GA lesion size (mm^2), mean (SD)		8.18 (3.893)	8.29 (3.904)	8.20 (3.722)
Square root GA lesion size (mm), mean (SD)		2.78 (0.682)	2.80 (0.674)	2.79 (0.649)
GA lesion size, n (%)	<7.5 mm^2	101 (50.0%)	99 (48.3%)	104 (50.5%)
GA lesion location, n (%)	Extrafoveal	**86 (42.6%)**	74 (36.1%)	60 (29.1%)
GA lesion focality, n (%)	Unifocal	59 (29.2%)	62 (30.2%)	68 (33.0%)
Intermediate/large drusen, n (%)	>20	93 (46.0%)	104 (50.7%)	103 (50.0%)
NL-BCVA (ETDRS letters), mean (SD)		61.0 (15.30)	58.2 (17.03)	57.5 (16.57)

These analyses were performed on the modified intent-to-treat (mITT) population. The mITT population was defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion area in the study eye.

ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; mm=millimeters; n=number of patients; NL-BCVA=normal luminance best-corrected visual acuity; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; ROW=rest of world; SD=standard deviation; US=United States.

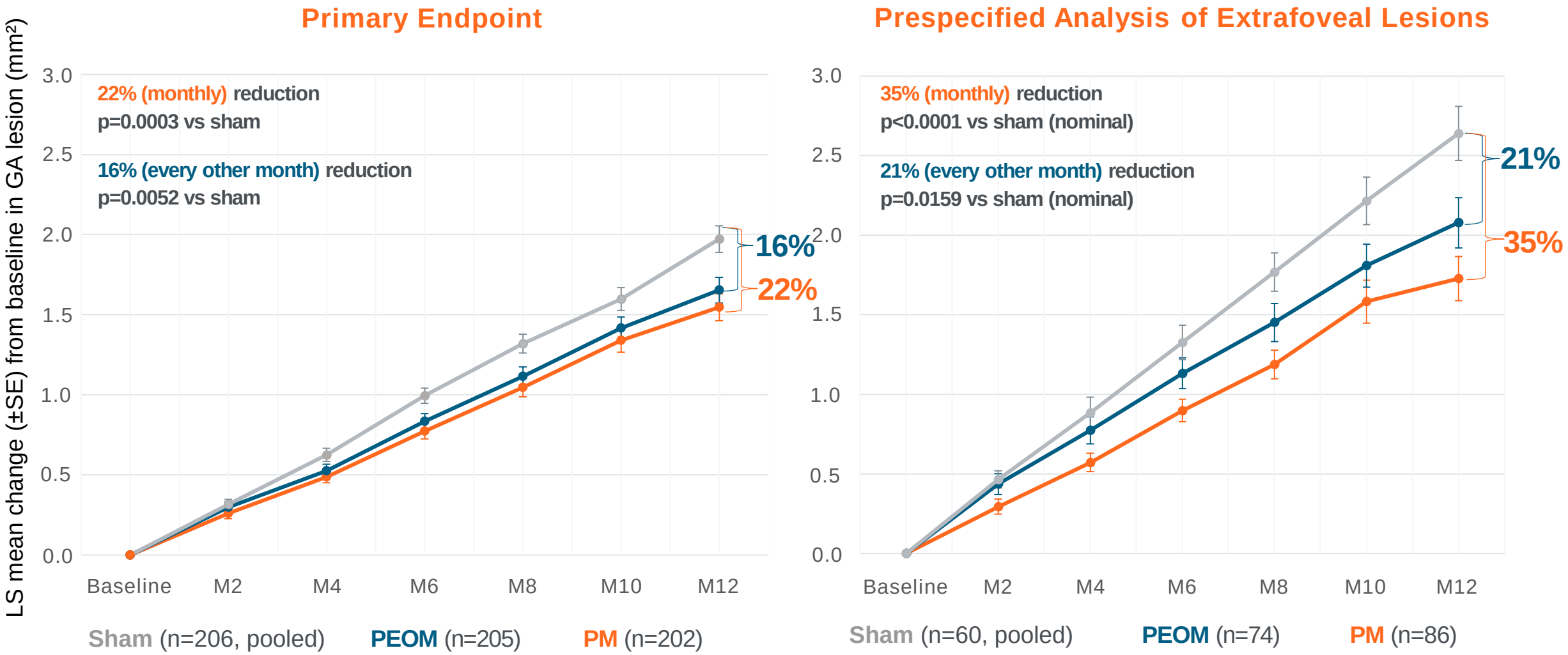
Key demographics and baseline study eye characteristics

		DERBY		
Characteristic		PM (N=201)	PEOM (N=200)	Sham Pooled (N=194)
Age, mean (SD)		78.7 (6.91)	79.2 (7.07)	78.6 (7.29)
Female, n (%)		118 (58.7%)	120 (60.0%)	122 (62.9%)
Male, n (%)		83 (41.3%)	80 (40.0%)	72 (37.1%)
Geographic region				
US, n (%)		142 (70.6%)	122 (61.0%)	122 (62.9%)
ROW, n (%)		59 (29.4%)	78 (39.0%)	72 (37.1%)
Caucasian, n (%)		187 (93.0%)	185 (92.5%)	187 (96.4%)
GA lesion size (mm^2), mean (SD)		8.36 (4.182)	8.22 (3.886)	8.26 (4.260)
Square root GA lesion size (mm), mean (SD)		2.80 (0.723)	2.79 (0.677)	2.78 (0.734)
GA lesion size, n (%)	<7.5 mm^2	99 (49.3%)	98 (49.0%)	94 (48.5%)
GA lesion location, n (%)	Extrafoveal	72 (35.8%)	81 (40.5%)	73 (37.6%)
GA lesion focality, n (%)	Unifocal	54 (26.9%)	53 (26.5%)	**66 (34.0%)**
Intermediate/large drusen, n (%)	>20	78 (38.8%)	78 (39.0%)	**98 (50.5%)**
NL-BCVA (ETDRS letters), mean (SD)		59.5 (17.40)	58.9 (15.97)	59.1 (16.85)

These analyses were performed on the modified intent-to-treat (mITT) population. The mITT population was defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion area in the study eye.

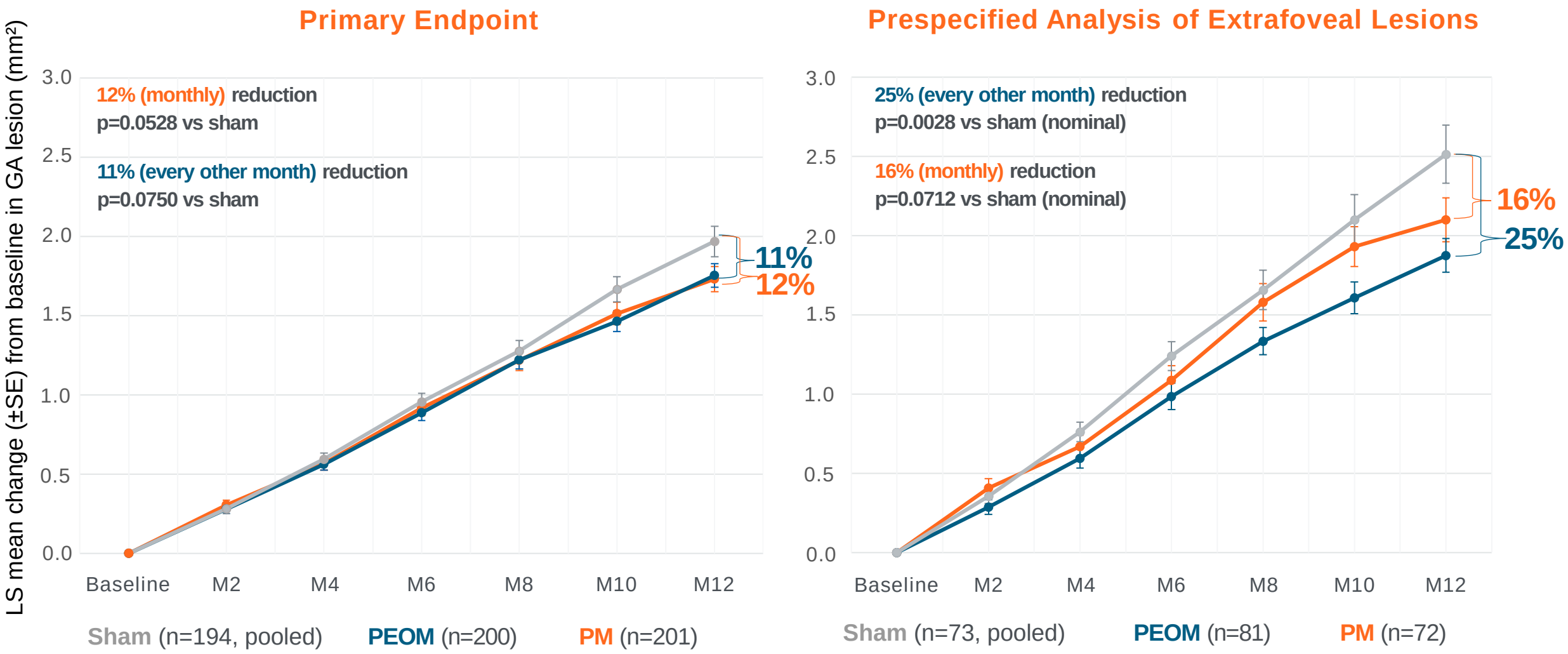
ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; mm=millimeters; n=number of patients; NL-BCVA=normal luminance best-corrected visual acuity; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; ROW=rest of world; SD=standard deviation; US=United States.

OAKS: Pegcetacoplan met the primary endpoint and further reduced lesion growth in patients with extrafoveal lesions



LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

DERBY: Pegcetacoplan did not meet the primary endpoint and reduced lesion growth in patients with extrafoveal lesions

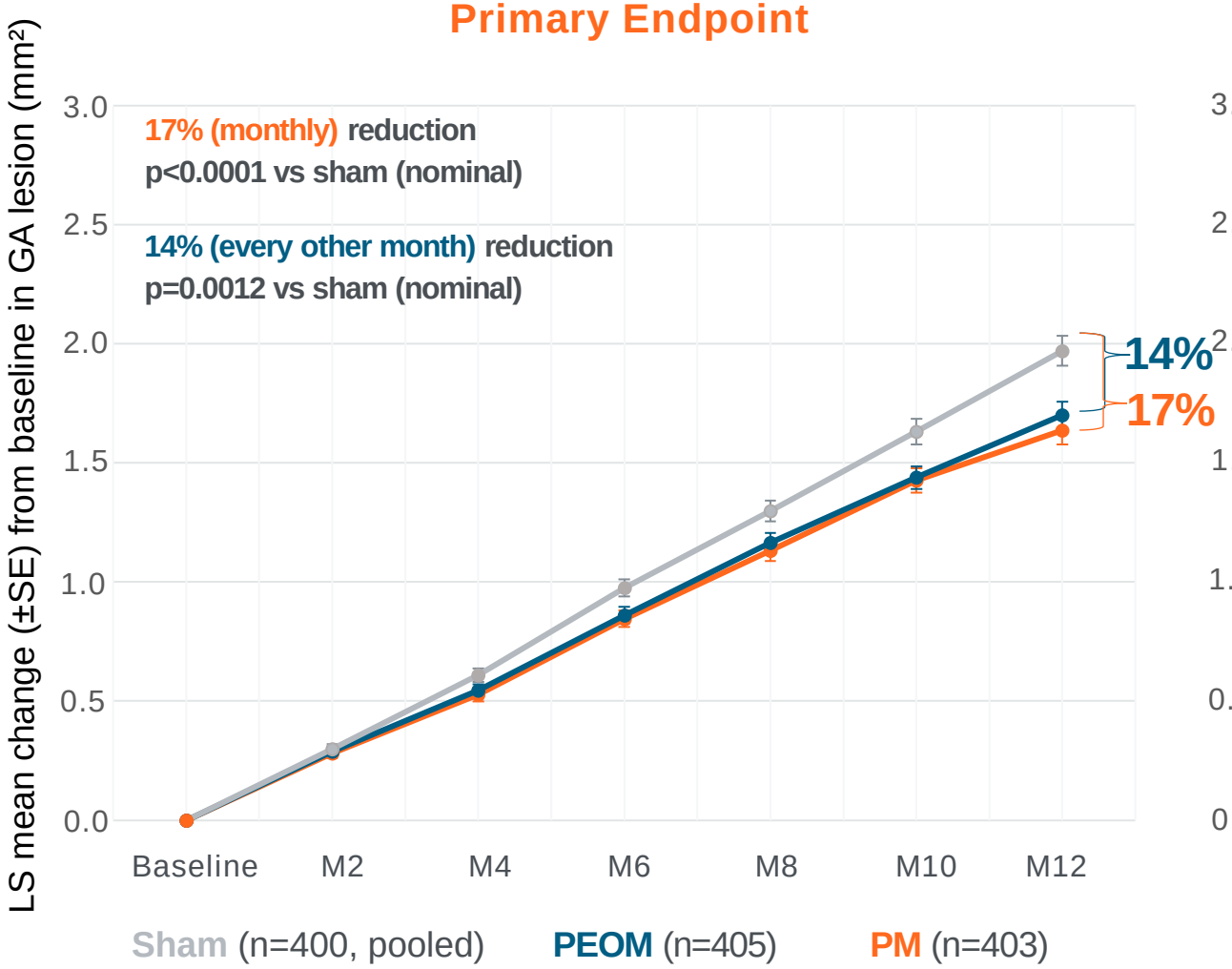


LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

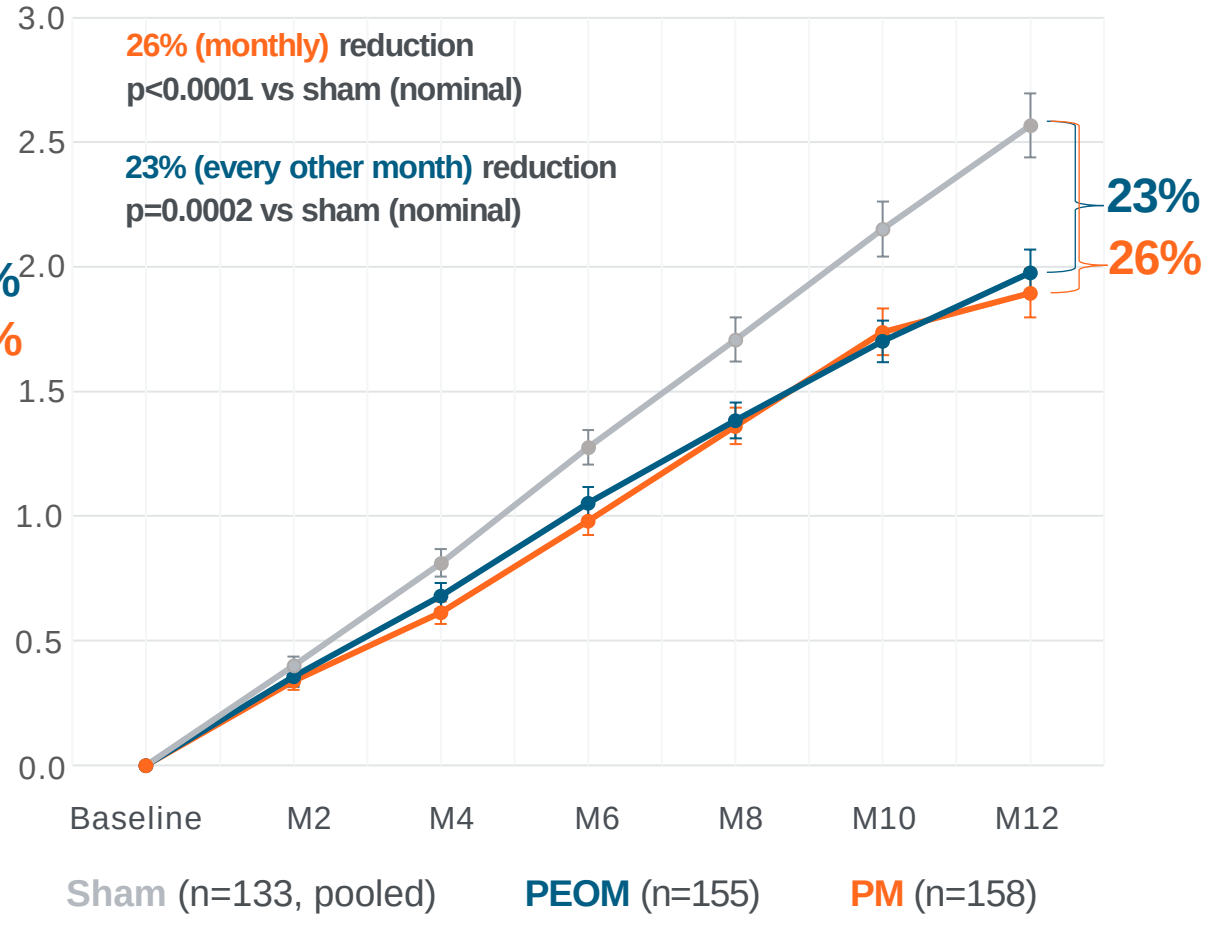
OAKS and DERBY: Pegcetacoplan reduced lesion growth in prespecified combined analyses of the primary endpoint and in extrafoveal lesions

OAKS DERBY

Primary Endpoint



Prespecified Analysis of Extrafoveal Lesions



LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Post-hoc covariate analysis:
What is the real effect size of pegcetacoplan?

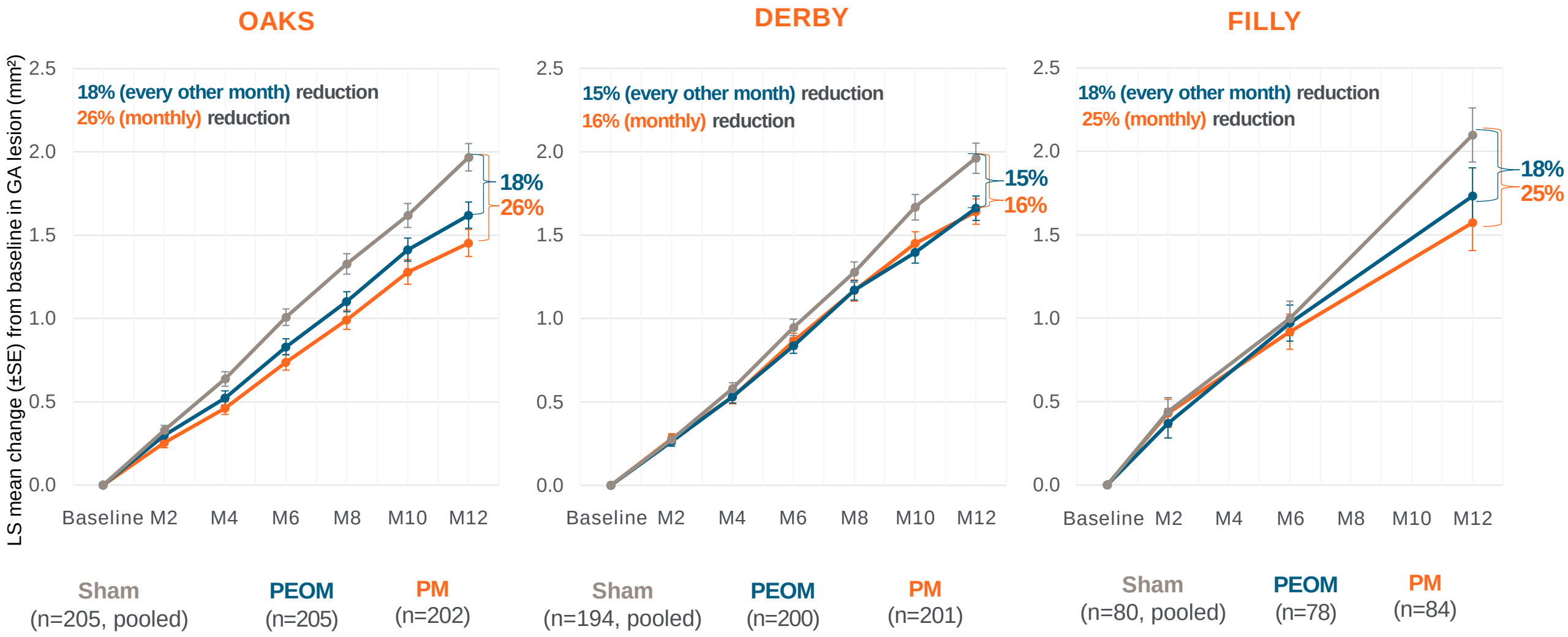
To examine potential contributions of baseline imbalances on diverging results, the 8 most relevant variables related to GA were investigated for imbalance, and analyses were re-run adjusting for the imbalanced variables:

Study eye focality • Imbalanced in DERBY (*favoring sham*) **Study eye lesion location** • Imbalanced in OAKS (*favoring sham*) **Study eye lesion size** **Study eye pseudodrusen**	**Study eye low luminance deficit** • Imbalanced in FILLY (*favoring PM*) **GA laterality** **Study eye intermediate/large drusen** • Imbalanced in DERBY (*favoring sham*) and FILLY (favo*ring PEOM*) **Region**

- All variables in red were adjusted for in all 3 studies

GA=geographic atrophy; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

Converging treatment effect of pegcetacoplan across OAKS, DERBY & FILLY in covariate-adjusted post-hoc analysis



LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis.
LS=least squares; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly; SE=standard error.

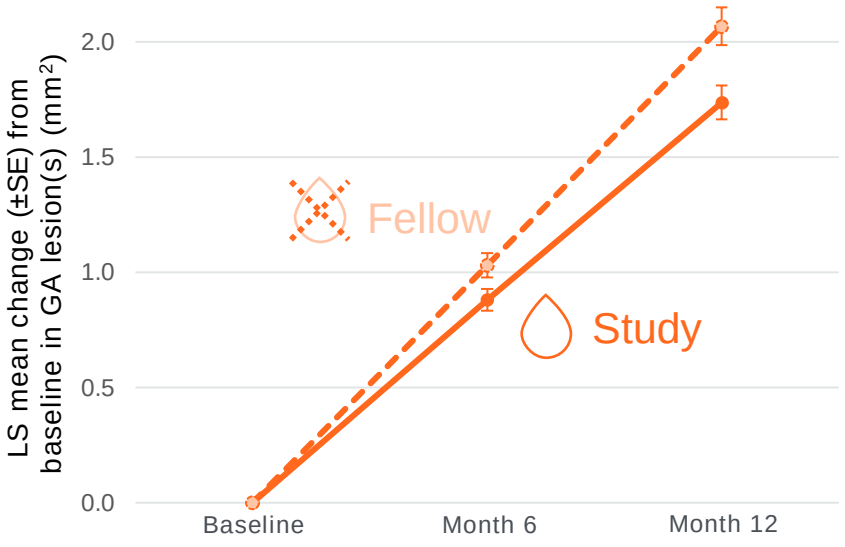
Pegcetacoplan reduced lesion growth in an analysis of study eyes vs. untreated fellow eyes, supporting primary analysis

DERBY OAKS

All data represented are from DERBY and OAKS combined

Pegcetacoplan
monthly

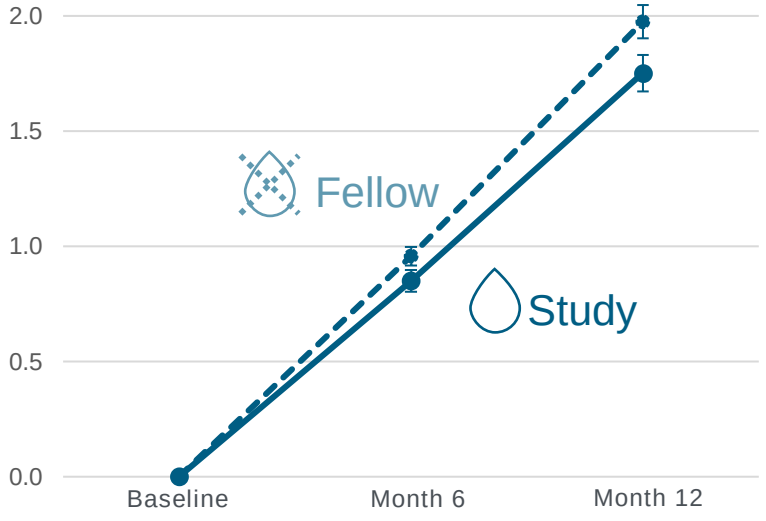
16% slower growth vs fellow eye
p<0.0001



n=177

Pegcetacoplan
every other month

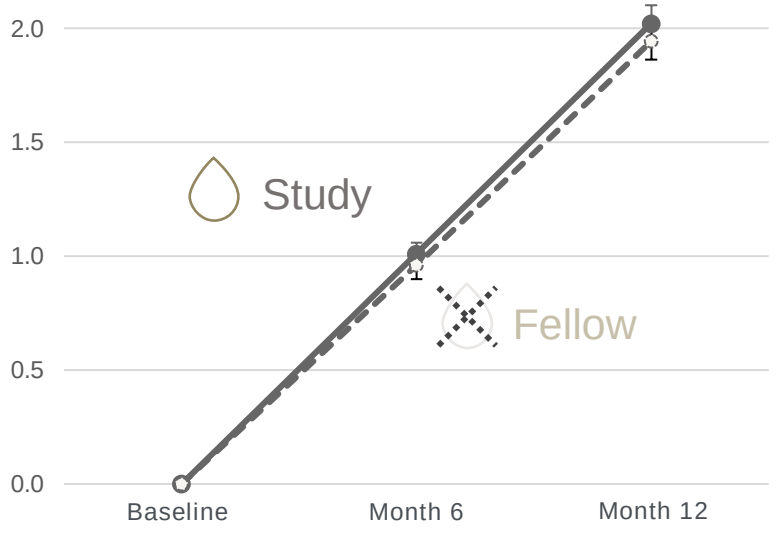
11% slower growth vs fellow eye
p=0.0011



n=211

Sham
pooled

4% faster growth vs fellow eye
p=0.2666



n=195

Study eye vs. fellow eye comparison was prespecified; statistical modeling was performed post-hoc. LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis. In addition, patients must have bilateral GA and a fellow eye that meets the following key characteristics at baseline: absence of CNV in the medical history; baseline GA lesion size between 2.5 and 17.5 mm^2 and have at least one study eye or fellow eye at measurement at Month 6 or Month 12.

CNV=choroidal neovascularization; GA=geographic atrophy; LS=least squares; SE=standard error.

Safety

Overall TEAEs

Note: Sham patients do not receive injections

	OAKS			DERBY		
	PM (N=213)	PEOM (N=212)	Sham Pooled (N=211)	PM (N=206)	PEOM (N=208)	Sham Pooled (N=206)
All TEAEs, n (%)	170 (79.8%)	160 (75.5%)	154 (73.0%)	158 (76.7%)	155 (74.5%)	145 (70.4%)
Total events, M	751	721	666	708	600	530
Ocular TEAEs in study eye						
Patients, n (%) M	108 (50.7%) 256	97 (45.8%) 208	74 (35.1%) 159	100 (48.5%) 227	91 (43.8%) 162	72 (35.0%) 126
Non-ocular TEAEs						
Patients, n (%) M	136 (63.8%) 390	127 (59.9%) 412	125 (59.2%) 413	127 (61.7%) 396	110 (52.9%) 339	112 (54.4%) 329
Serious ocular TEAEs in the study eye, n (%) M	3 (1.4%) 3	4 (1.9%) 4	0	1 (0.5%) 1	0	2 (1.0%) 2
Optic ischemic neuropathy	1 (0.5%) 1	0	0	0	0	0
Papilledema	1 (0.5%) 1	0	0	0	0	0
Retinal detachment	0	1 (0.5%) 1	0	0	0	0
Endophthalmitis[a]	1 (0.5%) 1	3 (1.4%) 3	0	0	0	0
Vitritis	0	0	0	1 (0.5%) 1	0	0
Dry AMD	0	0	0	0	0	1 (0.5%) 1
Macular hole	0	0	0	0	0	1 (0.5%) 1

[a]The events of endophthalmitis include infectious and noninfectious endophthalmitis.
Any AEs with missing or unknown severity were considered as severe. The safety population was used for this analysis.
AE=adverse event; AMD=age-related macular degeneration; M=number of events; n=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; TEAE=treatment-emergent AE.

Intraocular inflammation

	OAKS & DERBY combined		
	PM (N=419)	PEOM (N=420)	Sham Pooled (N=417)
Patients with ≥1 event of IOI, n (%)	9 (2.1%)	4 (1.0%)	0
Cases of IOI, n (%)			
Vitritis	5 (1.2%)	0	0
Iridocyclitis	2 (0.5%)	2 (0.5%)	0
Iritis	2 (0.5%)	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

- Total number of patients receiving pegcetacoplan experiencing IOI: 13 (1.5%)
- Rate of IOI per injection: 0.22%
- Four cases, including noninfectious (culture negative) endophthalmitis, were reported in 2018 and linked to drug impurity
- There were no cases of vasculitis or occlusive vasculitis
- **Majority of cases were mild, and 10/13 (77%) patients resumed IP administration, without IOI recurrence**

The safety population was used for this analysis.
IOI=intraocular inflammation; IP=investigational product; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

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

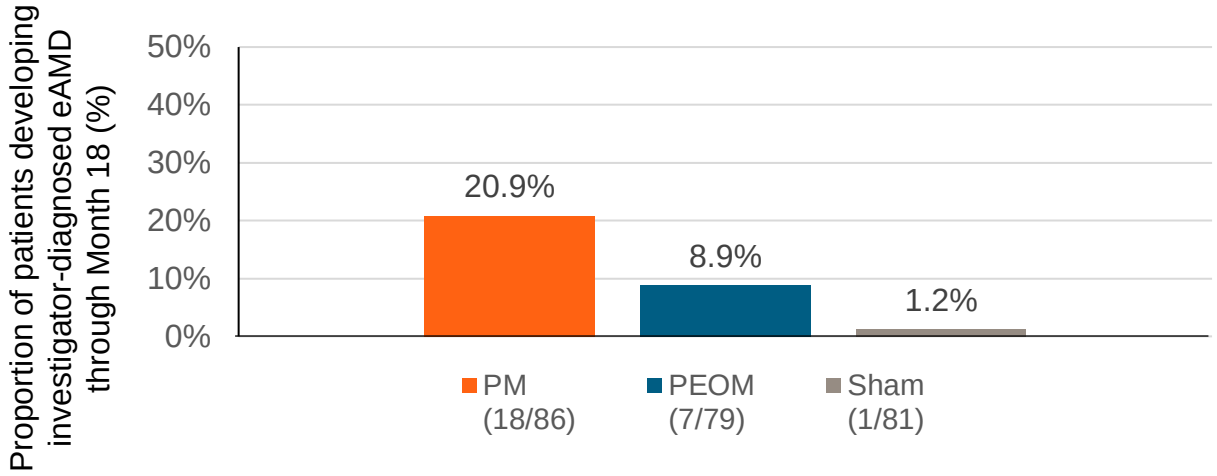
- Two cases with culture positive for Gram-positive bacteria; one case with no culture results
- All patients treated with IVT antibiotics; one case also treated with PPV
- Favorable visual acuity outcomes for all patients
- Rate of infectious endophthalmitis per injection: 0.047%
- Rate of infectious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

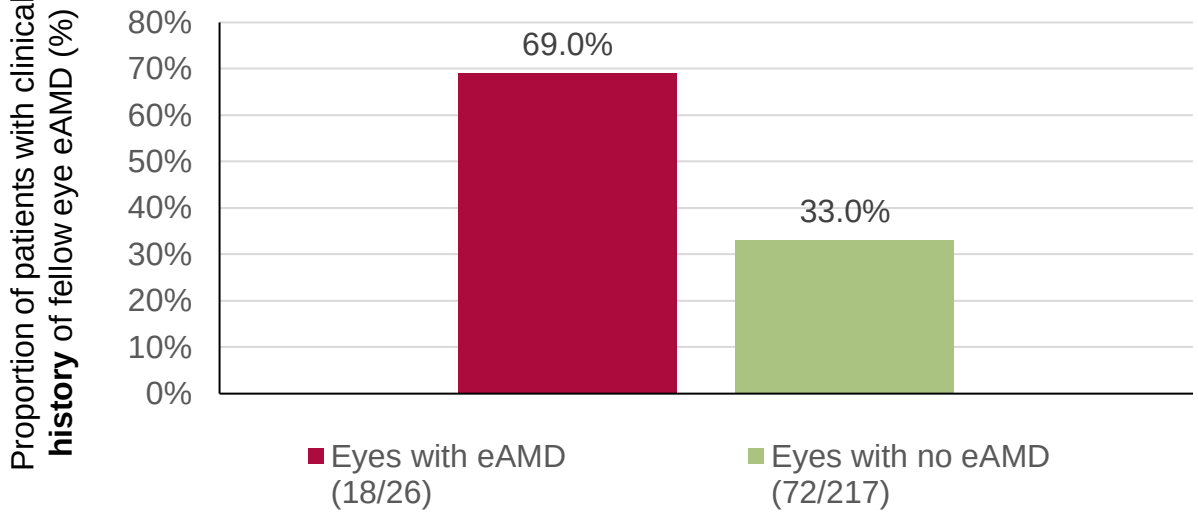
The safety population was used for this analysis.
IVT=intravitreal; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; PPV=pars plana vitrectomy.

Phase 2 FILLY trial: New-onset study eye eAMD

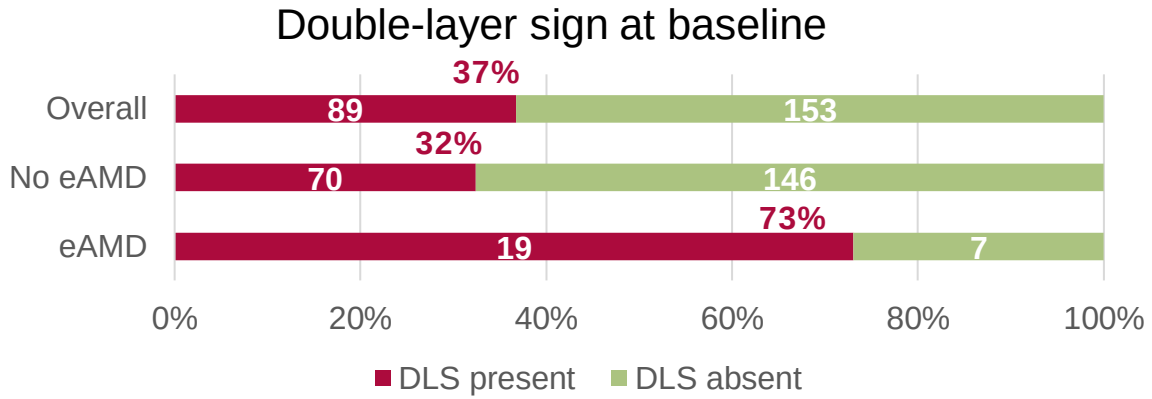
Characterizing New-Onset Exudation in the Randomized Phase 2 FILLY Trial of Complement Inhibitor Pegcetacoplan for Geographic Atrophy

Charles C. Wykoff, MD, PhD,[1] Philip J. Rosenfeld, MD, PhD,[2] Nadia K. Waheed, MD, MPH,[3] Rishi P. Singh, MD,[4] Nick Ronca, MS,[5] Jason S. Slakter, MD,[6] Giovanni Staurenghi, MD,[7] Jordi Monés, MD, PhD,[8] Caroline R. Baumal, MD,[3] Namrata Saroj, OD,[9] Ravi Metlapally, PhD,[5] Ramiro Ribeiro, MD, PhD[5]





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



DLS=double-layer sign; eAMD=exudative age-related macular degeneration; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SD-OCT=spectral domain optical coherence tomography.
Wykoff CC, et al. Ophthalmology 2021;128:1325–36.

eAMD evaluation in the phase 3 program

Reading center (DARC) and grading methodology is exactly the same across FILLY, OAKS, and DERBY

Adverse events of eAMD:

- During the study, if eAMD is suspected by an Investigator, prespecified imaging (CFP, OCT, FA & OCTA [select sites]) was acquired and sent to reading center
- The responsibility to report eAMD-related AEs and to start treatment with anti-VEGF was solely that of the Investigator, regardless of reading center confirmation
- Patients who developed eAMD continued treatment with on-label anti-VEGF therapy while remaining on study treatment

Reading center-determined cases not reported by investigators as AEs:

- Cases of MNV detected by the reading center by FA at Month 12, but not reported by investigators as adverse events, are also captured

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

Characteristics of eAMD[a]

COMBINED STUDIES	PM (N=419)	PEOM (N=420[b])	Sham Pooled (N=417)
Patients with study eye investigator-determined new-onset eAMD, n (%)	25 (6.0%)	17 (4.1%)	10 (2.4%)
Cases of MNV (FA) detected by reading center but not reported by investigator as AE	2	4	6
Sum of investigator-determined eAMD and reading center cases not reported by investigators	27 (6.4%)	21 (5.0%)	16 (3.8%)

- Six out of 52 investigator-determined cases of study eye eAMD were not confirmed by the reading center, but are included in the above totals
- Patients who developed eAMD continued treatment with pegcetacoplan and received anti-VEGF therapy per the label
- No impact of development of eAMD on efficacy of pegcetacoplan

[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.
[b]One patient had CNV on medical history in study eye and is not counted in the denominator for this analysis. 419 patients in the PEOM group were at risk of new-onset eAMD. The safety population was used for this analysis.
AE=adverse event; AMD=age-related macular degeneration; eAMD=exudative AMD; FA=fluorescein angiography; MNV=macular neovascularization; n=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan every month; VEGF=vascular endothelial growth factor.

Conclusions

- Pegcetacoplan monthly and every other month met the primary endpoint in OAKS
- Pegcetacoplan monthly and every other month did not meet the primary endpoint in DERBY
- Pegcetacoplan demonstrated greater efficacy in patients with extrafoveal lesions at baseline
- In a post-hoc analysis, after correcting for disparities in baseline characteristics, OAKS, DERBY, and FILLY results are more convergent
- OAKS, DERBY, and FILLY all show consistent efficacy of pegcetacoplan in treated study eyes versus untreated fellow eyes
- Overall, pegcetacoplan administered monthly or every other month was well tolerated in patients with GA
  - Majority of IOI cases were mild, and most patients resumed IP administration
  - 6.0%, 4.1%, and 2.4% of patients in the combined PM, PEOM, and sham groups experienced new-onset investigator-determined eAMD
- FDA submission is planned for the first half of 2022

eAMD=exudative age-related macular degeneration; FDA=Food and Drugs Administration; GA=geographic atrophy; IOI=intraocular inflammation; IP=investigational product; PEOM=pegcetacoplan every other month; PM=pegcetacoplan every month

Thank you to all the patients and sites around the world