Financial Disclosure

- I have the following financial interests or relationships to disclose:
  - Adverum Biotechnologies, Aerie Pharmaceuticals, Inc., Aerpio, Alcon Laboratories, Inc., Alkahest, Allergan, Allgenesis, Amgen, Annexon, Apellis, AsclepiX Therapeutics, Bausch+Lomb, Bayer Healthcare Pharmaceuticals, Biogen Inc., BioMotiv, BioTime, Inc., Boehringer-Ingelheim Pharmaceuticals, Cell Cure, Chengdu Kanghong Biotec, Clearside, CoDa Therapeutics, Daiichi Sankyo Co. LTD, Duet, Everads Therapy, LTD, EyePoint Pharmaceuticals, Foresight Biotherapeutics, Galimedix Therapeutics, GENENTECH, GenSight Biologics, GLAUKOS, GrayBug Vision, Iconic Therapeutics, Interface Biologics, Inc., Ionis, Iveric, Kala Pharmaceuticals, LumiThera, Inc., Nanoscope, Neurotech, NGM Bio, Notal Vision, Inc., Ocular Therapeutics, Ocuphire,Opthea, Optos, Inc., Optovue, Ora, Orbit Biomedical, Oxurion, RecensMedical Inc., Regeneron Pharmaceuticals, Inc., Regenxbi, Regulus Therapeutics, River Vision, Samumed, LLC, Santen, Inc., SciFluor, Semathera, Smilebiotek, Stealth BioTherapeutics, Sun Pharmaceutical Industries,Taiwan Liposomal Company, THEA, ThromboGenics, Unity: Consultant/Advisor
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Safety of Intravitreal Pegcetacoplan in Geographic Atrophy: 24-Month Results from the Phase 3 OAKS and DERBY Trials

David S. Boyer, Rishi P. Singh, Eleonora G. Lad, Frank G. Holz, Caleb Bliss, Robyn H. Guymer, Jordi M. Mones, Allen Hu, Anibal Francone, Jeffrey S. Heier, Charles C. Wykoff, Ramiro Ribeiro

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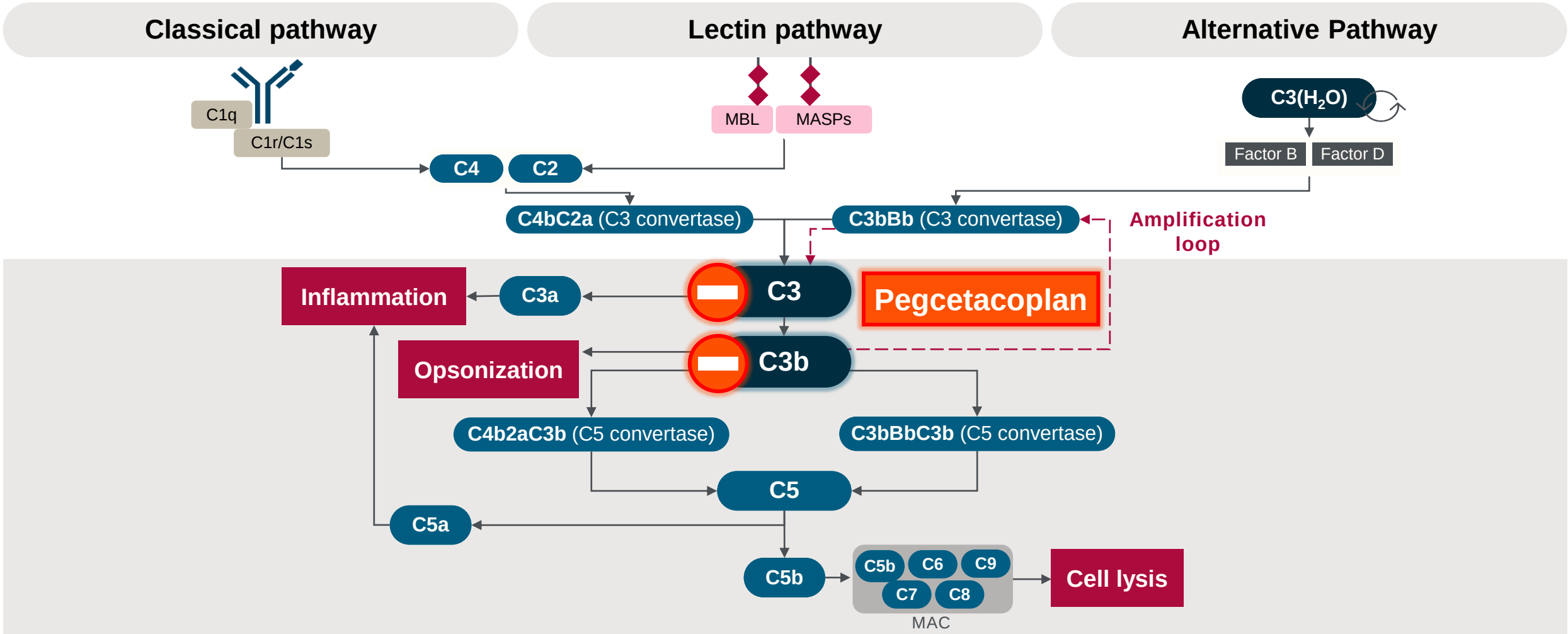
Pegcetacoplan binds to C3 and C3b, inhibiting the downstream effects of the complement pathway[1–6]



MAC=membrane attack complex; MBL=mannose-binding lectin; MASP=MBL-associated serine protease.

1. Kolev M et al. *Nat Rev Immunol* 2014;14:811–20; 2. Holers VM. *Annu Rev Immunol* 2014;32:433–59; 3. Dunkelberger JR, Song WC. *Cell Res* 2010;20:34–50; 4. Strunz T et al. *Sci Rep* 2020;10:1584; 5. Anderson DH et al. *Am J Ophthalmol* 2002;134:411–31; 6. Boyer DS et al. *Retina* 2017;37:819–35.

Design of the Phase 3 OAKS and DERBY studies

OAKS DERBY

Patients with GA secondary to AMD
~1200 patients at ~200 sites in the combined studies (1258 randomized in total)

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

Prespecified secondary endpoints at 24 months

- BCVA[a], LL-BCVA
- Reading speed[a]
- NEI VFQ-25
- FRI Index score[a]
- Microperimetry (OAKS only)[a] – MAIA device
- Lesion growth

GALE 3-year open-label extension study

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*

OAKS, DERBY, GALE CT.gov identifiers: NCT03525613, NCT03525600, NCT04770545, respectively. [a]Key secondary endpoints. AMD=age-related macular degeneration; BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; EOM=every other month; FRI=Functional Reading Independence; GA=geographic atrophy; LL=low luminance; MAIA=macular integrity assessment; MMRM=mixed-effects model for repeated measures; NEI-VFQ=National Eye Institute Visual Function Questionnaire.

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
  - GA lesions with or without subfoveal involvement 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, CNV in the study eye, including presence of RPE tear (assessed by reading center)

Ocular history of, or active, CNV in the fellow eye is not exclusionary

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

Key demographics and baseline study eye characteristics

Characteristic	OAKS		
	PM (N=202)	PEOM (N=205)	Sham Pooled (N=207)
Age, mean (SD)	78.8 (7.24)	78.1 (7.74)	78.6 (7.25)
Female, n (%)	125 (61.9%)	117 (57.1%)	133 (64.3%)
Male, n (%)	77 (38.1%)	88 (42.9%)	74 (35.7%)
Geographic region			
US, n (%)	147 (72.8%)	142 (69.3%)	148 (71.5%)
ROW, n (%)	55 (27.2%)	63 (30.7%)	59 (28.5%)
Caucasian, n (%)	185 (91.6%)	189 (92.2%)	188 (90.8%)
GA lesion size (mm^2), mean (SD)	8.18 (3.895)	8.30 (3.904)	8.21 (3.712)
Square root GA lesion size (mm), mean (SD)	2.78 (0.682)	2.80 (0.674)	2.79 (0.647)
GA lesion size <7.5 mm^2, n (%)	101 (50.0%)	98 (47.8%)	104 (50.2%)
Nonsubfoveal / extrafoveal lesion (location), n (%)	**86 (42.6%)**	**74 (36.1%)**	**60 (29.0%)**
Unifocal lesion (focality), n (%)	59 (29.2%)	62 (30.2%)	68 (32.9%)
Intermediate/large drusen >20, n (%)	93 (46.0%)	104 (50.7%)	104 (50.2%)
NL-BCVA (ETDRS letters), mean (SD)	61.0 (15.30)	58.2 (17.03)	57.6 (16.59)

These analyses were performed on the 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; mITT=modified intent-to-treat; 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=201)	Sham Pooled (N=195)
Age, mean (SD)	78.7 (6.91)	79.2 (7.08)	78.6 (7.28)
Female, n (%)	118 (58.7%)	120 (59.7%)	123 (63.1%)
Male, n (%)	83 (41.3%)	81 (40.3%)	72 (36.9%)
Geographic region			
US, n (%)	142 (70.6%)	122 (60.7%)	122 (62.6%)
ROW, n (%)	59 (29.4%)	79 (39.3%)	73 (37.4%)
Caucasian, n (%)	187 (93.0%)	186 (92.5%)	188 (96.4%)
GA lesion size (mm^2), mean (SD)	8.37 (4.181)	8.25 (3.894)	8.24 (4.261)
Square root GA lesion size (mm), mean (SD)	2.80 (0.722)	2.79 (0.678)	2.78 (0.734)
GA lesion size <7.5 mm^2, n (%)	99 (49.3%)	98 (48.8%)	95 (48.7%)
Nonsubfoveal / extrafoveal lesion (location), n (%)	**72 (35.8%)**	**81 (40.3%)**	**73 (37.4%)**
Unifocal lesion (focality), n (%)	54 (26.9%)	53 (26.4%)	66 (33.8%)
Intermediate/large drusen >20, n (%)	78 (38.8%)	78 (38.8%)	98 (50.3%)
NL-BCVA (ETDRS letters), mean (SD)	59.5 (17.40)	58.7 (16.12)	59.0 (16.85)

These analyses were performed on the 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; mITT=modified intent-to-treat; 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.

Patient disposition and exposure at Month 24

	OAKS			DERBY		
ITT set	PM (N=213)	PEOM (N=212)	Sham Pooled (N=212)	PM (N=206)	PEOM (N=208)	Sham Pooled (N=207)
Completed study through Month 24, n (%)	144 (67.6%)	169 (79.7%)	158 (74.5%)	147 (71.4%)	161 (77.4%)	161 (77.8%)
Discontinued study prior to Month 24, n (%)	69 (32.4%)	43 (20.3%)	54 (25.5%)	59 (28.6%)	47 (22.6%)	46 (22.2%)

19% (60/318) of study discontinuations were attributed to COVID-19

mITT set	PM (N=202)	PEOM (N=205)	Sham Pooled (N=207)	PM (N=201)	PEOM (N=201)	Sham Pooled (N=195)
Mean number of injections/patient, n (SD)	18.9 (6.08)	10.2 (2.92)	14.4 (6.50)	18.7 (6.09)	10.0 (2.80)	14.7 (6.46)
Mean compliance, %	87.4%	90.5%	87.9%	85.6%	89.0%	88.7%

Compliance % = injections administered/injections scheduled up to study completion or treatment discontinuation x 100

The ITT set includes all randomized patients. mITT = modified ITT, 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 geographic atrophy lesion area in the study eye. ITT=intent-to-treat; N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SD=standard deviation.

TEAEs in OAKS over 24 months

	OAKS		
	PM (N=213)	**PEOM (N=212)**	**Sham pooled (N=211)**
All TEAEs, n (%)	192 (90.1%)	187 (88.2%)	175 (82.9%)
Ocular TEAEs in study eye			
Patients, n (%)	133 (62.4%)	123 (58.0%)	98 (46.4%)
Non-ocular TEAEs			
Patients, n (%)	174 (81.7%)	165 (77.8%)	154 (73.0%)
Serious ocular TEAEs in the study eye, n (%) M	5 (2.3%) 7	4 (1.9%) 4	1 (0.5%) 1
Optic ischemic neuropathy	2 (0.9%) 2	0	0
Retinal detachment	1 (0.5%) 1	1 (0.5%) 1	0
Papilledema	1 (0.5%) 1	0	0
Visual acuity reduced	0	0	1 (0.5%) 1
Endophthalmitis	2 (0.9%) 2	3 (1.4%) 3	0
Hyphema	1 (0.5%) 1	0	0

Safety set. Note that n indicates the number of patients. M indicates number of events.
The events of endophthalmitis include infectious and noninfectious endophthalmitis. Sham patients do not receive injections.
N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; TEAE=treatment-emergent adverse event.

Most common ocular AEs in the study eye (≥5% in OAKS) over 24 months

	OAKS		
	PM (N=213)	**PEOM (N=212)**	**Sham pooled (N=211)**
Number of patients with ≥1 ocular TEAE in the study eye, n (%) M	133 (62.4%) 399	123 (58.0%) 313	98 (46.4%) 236
Ocular TEAEs in study eye in ≥5% of pegcetacoplan patients, n (%) M			
Conjunctival hemorrhage	22 (10.3%) 39	19 (9.0%) 25	10 (4.7%) 10
Visual acuity reduced	17 (8.0%) 21	20 (9.4%) 21	18 (8.5%) 29
Vitreous floaters	17 (8.0%) 20	19 (9.0%) 25	2 (0.9%) 2
Neovascular AMD	20 (9.4%) 21	14 (6.6%) 15	3 (1.4%) 3
Eye pain	17 (8.0%) 19	16 (7.5%) 18	14 (6.6%) 18
Dry eye	14 (6.6%) 15	14 (6.6%) 15	7 (3.3%) 7
Punctate keratitis	16 (7.5%) 16	6 (2.8%) 6	0

Safety set. AEs that occurred in at least 5% of pooled pegcetacoplan patients are listed by preferred term. Note that n indic ates the number of patients. M indicates number of events. Sham patients do not receive injections.
AE=adverse event; AMD=age-related macular degeneration; N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; TEAE=treatment-emergent AE.

TEAEs in DERBY over 24 months

	DERBY		
	PM (N=206)	PEOM (N=208)	Sham pooled (N=206)
All TEAEs, n (%)	178 (86.4%)	180 (86.5%)	169 (82.0%)
Ocular TEAEs in study eye			
Patients, n (%)	125 (60.7%)	108 (51.9%)	95 (46.1%)
Non-ocular TEAEs			
Patients, n (%)	163 (79.1%)	142 (68.3%)	146 (70.9%)
Serious ocular TEAEs in the study eye, n (%) M	4 (1.9%) 4	2 (1.0%) 4	2 (1.0%) 2
Uveitis	0	2 (1.0%) 2	0
Vitritis	2 (1.0%) 2	0	0
Iridocyclitis	0	1 (0.5%) 1	0
Optic ischemic neuropathy	1 (0.5%) 1	0	0
Retinal tear	1 (0.5%) 1	0	0
Visual acuity reduced	0	1 (0.5%) 1	0
Dry AMD	0	0	1 (0.5%) 1
Macular hole	0	0	1 (0.5%) 1

Safety set. Note that n indicates the number of patients. M indicates number of events. Sham patients do not receive injections.
AE=adverse event; N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; TEAE=treatment-emergent AE.

Most common ocular AEs in the study eye (≥5% in DERBY) over 24 months

	DERBY		
	PM (N=206)	PEOM (N=208)	Sham pooled (N=206)
Number of patients with ≥1 ocular TEAE in the study eye, n (%) M	125 (60.7%) 354	108 (51.9%) 258	95 (46.1%) 184
Ocular TEAEs in study eye in ≥5% of pegcetacoplan patients, n (%) M			
Vitreous floaters	24 (11.7%) 29	10 (4.8%) 12	3 (1.5%) 3
Neovascular AMD	21 (10.2%) 22	10 (4.8%) 10	5 (2.4%) 6
Conjunctival hemorrhage	12 (5.8%) 16	15 (7.2%) 21	5 (2.4%) 6
Retinal hemorrhage	9 (4.4%) 9	15 (7.2%) 15	8 (3.9%) 9
Visual acuity reduced	16 (7.8%) 16	7 (3.4%) 9	10 (4.9%) 11
Vitreous detachment	8 (3.9%) 8	14 (6.7%) 14	6 (2.9%) 6
Eye pain	13 (6.3%) 18	8 (3.8%) 9	13 (6.3%) 15

Safety set. AEs that occurred in at least 5% of pooled pegcetacoplan patients are listed by preferred term. Note that n indic ates the number of patients. M indicates number of events. Sham patients do not receive injections.
AE=adverse event; AMD=age-related macular degeneration; N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; TEAE=treatment-emergent AE.

Events of infectious endophthalmitis over 24 months

OAKS and DERBY combined

	PM (N=419)	PEOM (N=420)	Sham Pooled (N=417)
Infectious endophthalmitis in study eye, n (%)	2 (0.5%)	2 (0.5%)	0

- 0.034% per injection (11,757 total injections administered)
- No new cases between Months 18–24

Safety set. One event of noninfectious (culture negative) endophthalmitis reported in 2018 and linked to drug impurity is counted as an IOI (see next slide).
IOI=intraocular inflammation; N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

Events of intraocular inflammation over 24 months

OAKS and DERBY combined

	PM (N=419)	PEOM (N=420)	Sham Pooled (N=417)
IOI in study eye, n (%) M*	16 (3.8%) 17	9 (2.1%) 11	1 (0.2%) 1

*Total includes four patients with events of IOI reported in 2018 and linked to drug impurity.
n indicates number of patients, M indicates number of events.

- 0.24% per injection including four IOI events in 2018 (28 events in PM + PEOM out of 11,757 injections)
- 19 (66%) events were mild, 4 (14%) moderate, 6 (21%) severe
  - Two of the patients with severe events were from 2018 and attributed to drug impurity
  - Two patients had >1 IOI event; each of the reported events occurred after the same injection in each patient
- 20 (77%) patients with IOI continued or resumed study drug; there was no subsequent recurrence of IOI after administration of pegcetacoplan was resumed. No patients discontinued the study due to IOI.
- No AEs of IOI reported to have retinal involvement
- **No reports of occlusive vasculitis or retinitis**

Safety set. *Cases of IOI include four events (including one event of noninfectious endophthalmitis) reported in 2018 and linked to drug impurity.
AE=adverse event; IOI=intraocular inflammation; N=number of patients; M=number of events; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

New-onset eAMD in study eye over 24 months[a]

OAKS DERBY

OAKS and DERBY combined

	PM (N=419)	PEOM (N=420)[b]	Sham Pooled (N=417)
New-onset investigator-determined eAMD in study eye, n (%)	**51 (12.2%)**	**28 (6.7%)**	**13 (3.1%)**
Confirmed by reading center, N (%) At time of investigator-reported eAMD, 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 eAMD in study eye regardless of reading center confirmation
- Patients who developed eAMD 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. [b]Number of patients at risk for new-onset eAMD in PEOM arms from OAKS and DERBY combined was 419. All data are from safety set. AE=adverse event; AMD=age-related macular degeneration; CNV=choroidal neovascularization; eAMD=exudative AMD; FA=fluorescein angiography; N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan every month; SD-OCT=spectral domain optical coherence tomography; VEGF=vascular endothelial growth factor.

Characteristics of eAMD in study eye: CNV type on FA[a] over 24 months

OAKS DERBY

OAKS and DERBY combined

	PM (N=35)	PEOM (N=23)	Sham Pooled (N=12)
CNV type on FA at eAMD study visit, n (%)			
No CNV	1 (2.9%)	1 (4.3%)	0
Classic	1 (2.9%)	1 (4.3%)	0
Occult	28 (80.0%)	21 (91.3%)	11 (91.7%)
Active leakage with low likelihood of CNV	5 (14.3%)	0	1 (8.3%)

- Table includes all events with available reading center determination of CNV type on FA at time of eAMD study visit

[a]Events include preferred terms of CNV and neovascular AMD.
Safety set. AE=adverse event; AMD=age-related macular degeneration; CNV=choroidal neovascularization; eAMD=exudative AMD; FA=fluorescein angiography; N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan every month.

Safety summary – OAKS and DERBY Phase 3 studies

- Overall, pegcetacoplan was well tolerated in patients with GA, with a safety profile generally consistent with trials of intravitreal therapeutics
  - Majority of IOI cases were mild, and most patients resumed IP administration
  - 12.2%, 6.7%, and 3.1% of patients in the combined monthly, EOM, and sham groups experienced new-onset investigator-determined eAMD
- GALE extension study will provide longer-term data through 5 years of treatment for both monthly and EOM dosing
- FDA review is ongoing with PDUFA target action date of November 26, 2022, and EMA submission is planned by end of 2022

eAMD=exudative age-related macular degeneration; EMA=European Medicines Agency; EOM=every other month; FDA=Food and Drug Administration; GA=geographic atrophy; IOI=intraocular inflammation; IP=investigational product; PDUFA=Prescription Drug User Fee Act.