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

David Boyer, Nathan Steinle, Charles Wykoff, Jeffrey Heier, Rishi Singh, Jordi Monés, Giovanni Staurenghi, Frank G. Holz, Caleb Bliss, Pascal Deschatelets, Federico Grossi, Cedric Francois, Ramiro Ribeiro

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Pegcetacoplan is an investigational product in geographic atrophy. The treatment discussed in the presentation is not an FDA-approved use of pegcetacoplan.

Disclosures

- Dr. Boyer has the following disclosures:
  - Consultant: 4DMT, Achillion Pharmaceuticals, Acucela, Adverum, Aerie, Aerpio, AiViva BioPharma, Alcon, Aldeyra, Alkahest, Allegro, Allergan, Allgenesis, Alzheon, Amgen, Amydis, Annexon, Apellis, Asclepix, Aviceda, Bausch & Lomb (Valeant), Bayer, Biogen, BioMotiv, Bionic Vision Technologies, BioTime, Biovisics Medical, Boehringer-Ingelheim Pharma, Boxer Capital, Cell Care Therapeutic, Chengdu Kanghong Biotechnology, Ciana Therapeutics, Clearside Biomedical, Daiichi Sankyo, Delsitech, Dark Horse, DTx, Duet Pharmaceuticals, Eloxx, Eyepoint, Galimedix, Genentech, GenSight, Glaukos, GlaxoSmithKline, Graybug, Gyroscope, Horizon, I2vision, Kala, Iconic, Interface, Ionis, Isarna,Iveric Bio, jCyte, Kanghong, LensGen, Lineage Cell, LumiThera, MantraBio, NGM, Notal Vision, Novartis, Ocular Therapeutix, Ocugen, Oculis, Ocuphire, OcuTerra, Opthea, OptoVue, Ora, Orbit, Oxurion, Palatin, Ray, Regeneron, Regenxbio, Regulus, RetinAI Medical, Ripple, Roche, Samumed, Santen, Shenyang XingQi, Semathera, Stealth, Surrozen, Thea, Unity, Verseon, Viewpoint, Vinci, and Vitranu.
  - Stock:Allegro and DigiSight (Verana Health).

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Overall AEs and SAEs

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.

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.

Cases of Intraocular Inflammation

Intraocular inflammation: 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

IP, investigational product.

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

- 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
- **Majority of cases were mild, and 10/13 patients resumed IP administration, without subsequent recurrence of IOI**

IOI=intraocular inflammation; IP=investigational product; 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-positive bacteria; 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

Nonexudative nAMD

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

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

João R. de Oliveira Dias, MD, PhD,[1] Qinqin Zhang, PhD,[2] José M.B. Garcia, MD,[1] Fang Zheng, MD,[1,3] Elie H. Motulsky, MD, PhD,[1] Luiz Roisman, MD, PhD,[1] Andrew Miller, MD,[1] Chieh-Li Chen, PhD,[2] Sophie Kubach, MS,[4] Luis de Sisternes, PhD,[4] Mary K. Durbin, PhD,[4] William Feuer, MS,[1] Ruikang K. Wang, PhD,[2] Giovanni Gregori, PhD,[1] Philip J. Rosenfeld, MD, PhD[1]

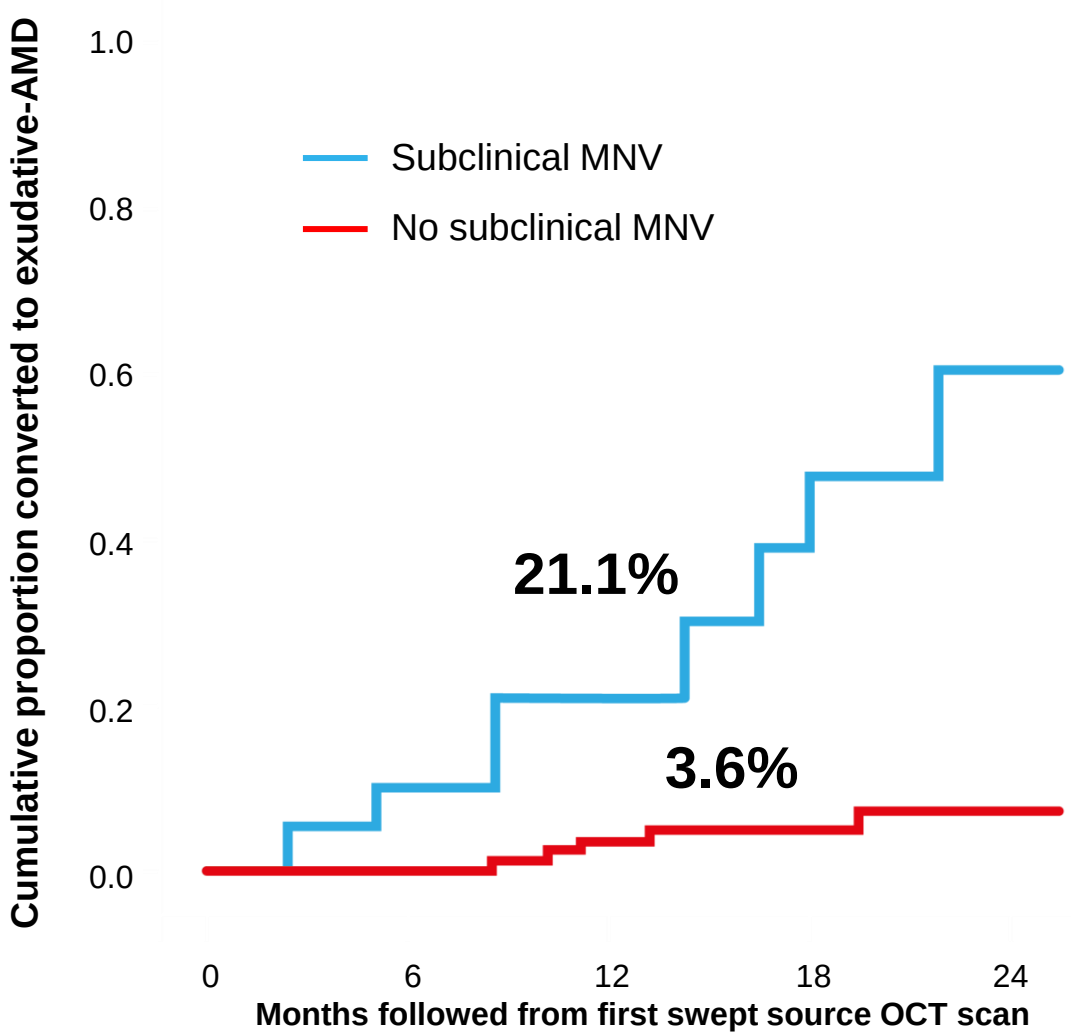
2018

160 eyes with intermediate dry AMD or GA

- 14.4% = subclinical MNV = nonexudative nAMD

Conversion to exudative AMD

- Subclinical MNV = increased risk of exudation



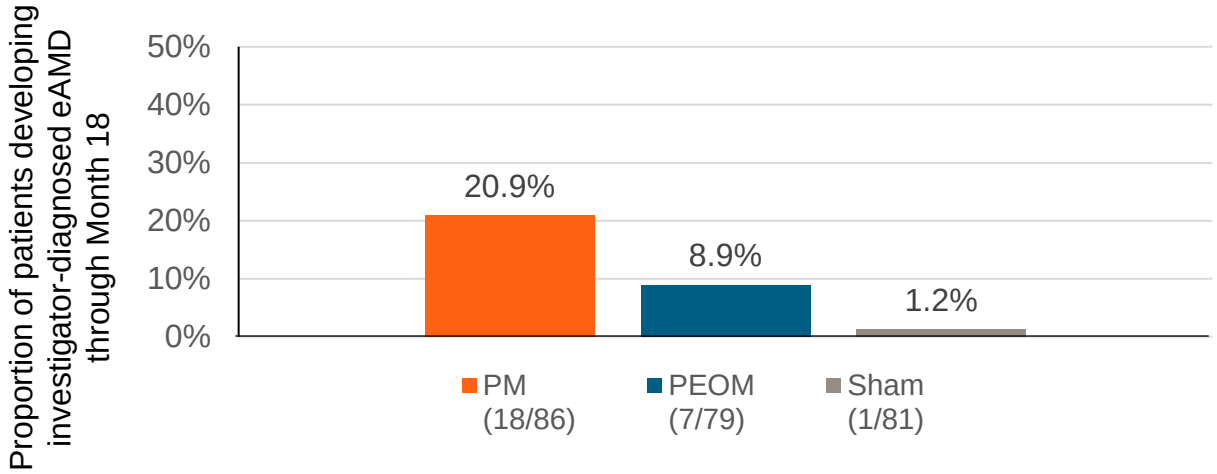
AMD=age-related macular degeneration; GA=geographic atrophy; MNV=macular neovascularization; nAMD=neovascular AMD; OCT=optical coherence tomography.

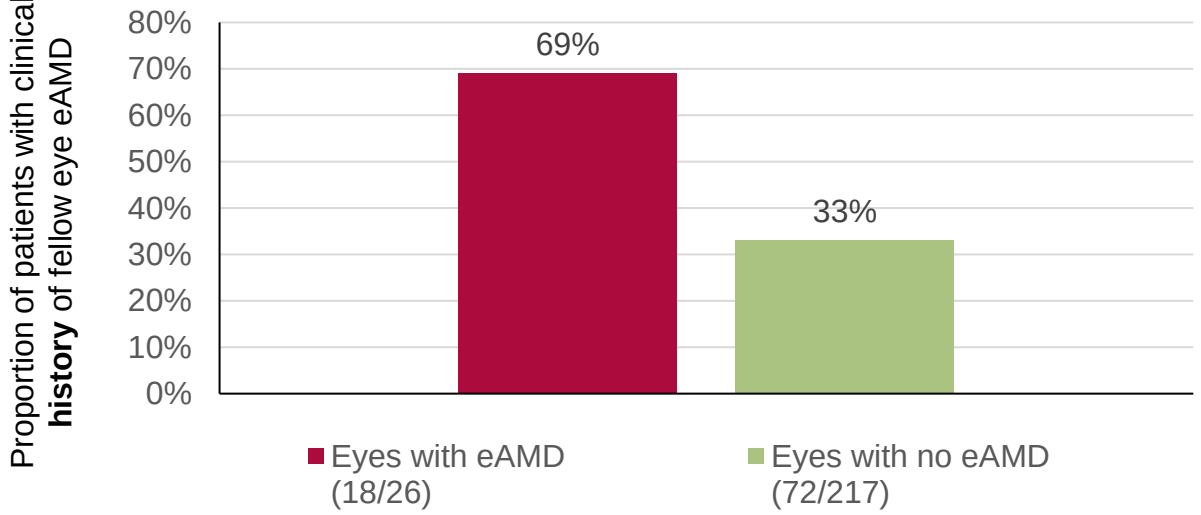
de Oliveira Dias JR et al. Ophthalmology 2018;125:255–66.

Phase 2 FILLY trial: New-onset study eye eAMD

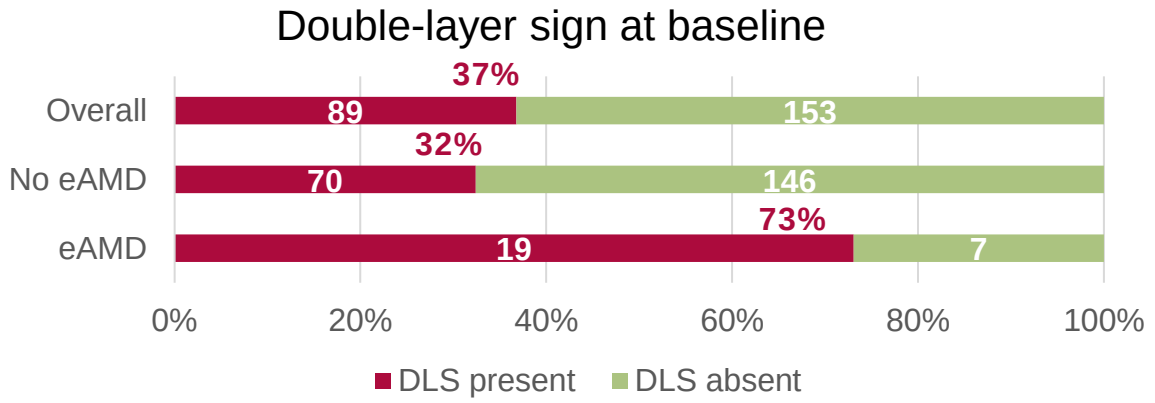
Characterizing New-Onset Exudation in the Randomized Phase 2 FILLY Trial of Complement Inhibitor Pegcetacoplan for Geographic Atrophy

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 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; 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 findings from FILLY informed the design of 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 was suspected by the 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 to the Investigator, regardless of reading center confirmation

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 reported

AMD=age-related macular degeneration; AEs=adverse events; 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
  - History of fellow eye eAMD not exclusionary
  - Across OAKS and DERBY study arms, between 18-21% of patients had fellow eye CNV present at baseline

- Study eye
  - Any history or evidence of active eAMD was exclusionary
  - Patients with subclinical MNV either by DLS or OCTA were not excluded
  - Across OAKS and DERBY study arms, between 14-20% of patients had study eye DLS present at baseline

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

Characteristics of eAMD[a]

	OAKS			DERBY		
	PM (N=213)	PEOM (N=212*)	Sham Pooled (N=211)	PM (N=206)	PEOM (N=208)	Sham Pooled (N=206)
Patients with **study eye** 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 (6.2%)	8 (3.8%)	14 (6.8%)	8 (3.8%)	8 (3.9%)

- **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**

[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.
*One patient had CNV on medical history in study eye and is not counted in the denominator for this analysis. 211 patients were at risk of new-onset eAMD.
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.

Rates of eAMD in the combined studies[a]

COMBINED STUDIES	PM (N=419)	PEOM (N=420*)	Sham Pooled (N=417)
Investigator-determined new-onset eAMD, %	6.0%	4.1%	2.4%
Total of Investigator- and Reading Center-determined new-onset eAMD, %	6.4%	5.0%	3.8%

[a]Events include preferred terms of choroidal neovascularization and neovascular AMD. FA was captured per protocol at Screening and Month 12.
*One patient had CNV on medical history in study eye and is not counted in the denominator for this analysis. 211 patients were at risk of new-onset eAMD.
AE=adverse event; AMD=age-related macular degeneration; eAMD=exudative AMD; FA=fluorescein angiography; n=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan every month.

Rate of eAMD by baseline fellow eye CNV status

	OAKS			DERBY		
	PM (N=213)	PEOM (N=212*)	Sham Pooled (N=211)	PM (N=206)	PEOM (N=208)	Sham Pooled (N=206)
With fellow eye CNV						
n/N	1/45	3/39	3/44	5/39	1/42	4/42
%	2.2%	7.7%	6.8%	12.8%	2.4%	9.5%
Without fellow eye CNV, n/N (%)						
n/N	10/168	7/172	0/167	9/167	6/166	3/164
%	6%	4.1%	0%	5.4%	3.6%	1.8%

*One patient had CNV on medical history in study eye and is not counted in the denominator for this analysis. 211 patients were at risk of new-onset eAMD.
CNV=choroidal neovascularization; eAMD=exudative age-related macular degeneration; N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan every month;

eAMD Summary

- eAMD rates reported here include all adverse events reported by investigators, whether or not there was reading center confirmation
- Cases detected by the reading center at the 12 month FA, but not reported as AEs by investigators, are also reported here, regardless of whether there was OCT confirmation
- Rates of eAMD were lower in OAKS and DERBY than in FILLY
  - Same definition of eAMD used across all three trials
  - Rate of fellow eye CNV at baseline is lower in OAKS and DERBY and closer to expected rates (~20%) as opposed to FILLY (35-42%)
  - eAMD rates in OAKS and DERBY reported over 12 months of follow up, as opposed to 18 months of follow up in FILLY
  - FA and OCT images sent to reading center to confirm eAMD diagnosis in OAKS and DERBY
  - Masking in OAKS and DERBY reduces potential investigator bias

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.

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
- Majority of IOI cases were mild, and most patients resumed IP administration
- Rate of endophthalmitis was 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.