Efficacy and Safety of Intravitreal Pegcetacoplan in GA: Results From the Phase 3 DERBY and OAKS Trials

Singh RP, Heier J, Wykoff C, et al. Presented at American Academy of Ophthalmology, New Orleans, LA; November 15, 2021.
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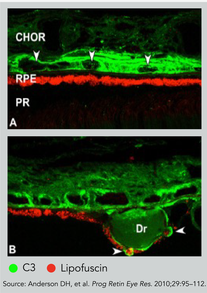
The DERBY and OAKS trials are Phase 3, randomized, double-masked, sham-controlled studies evaluating the efficacy and safety of intravitreal pegcetacoplan in patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Primary outcome measures are change in total area of GA lesion(s) in the study eye, from baseline to Month 12.

What evidence supports a relationship between excessive complement activation and geographic atrophy in AMD?

Histological — Complement proteins are present in drusen, choroid, and sub-RPE space[1]

Physiological — Elevated levels of complement activation products can be observed in the plasma and ocular tissues of patients with AMD[2]

Genetic — Variants in complement system genes have been implicated in AMD pathogenesis[3,4]

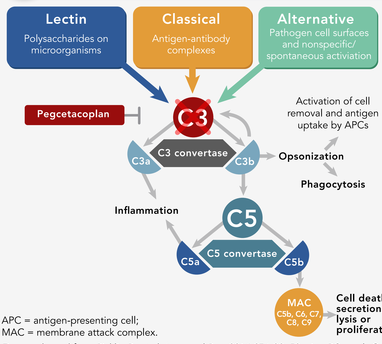


Source: Anderson DH, et al. *Prog Retin Eye Res.* 2010;29:95–112.

AMD = age-related macular degeneration; CHOR = choroid; Dr = drusen; RPE = retinal pigment epithelium; PR = photoreceptor layer.

1. Anderson DH, et al. *Am J Ophthalmol.* 2002;134:411–431; 2. Boyer DS, et al. *Retina.* 2017;37:819–835;
3. Handa JT, et al. *Nat Commun.* 2019;10:3347; 4. Fritsche LG, et al. *Nat Genet.* 2016;48:134–143.

Inhibition of the complement cascade provides a target: C3



Dysregulation of the complement cascade has been implicated in GA pathogenesis

All 3 complement pathways end in the central cleavage of C3

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

Inhibition of C3 blocks steps in the complement cascade needed for opsonization, inflammation, and formation of MAC

APC = antigen-presenting cell;
MAC = membrane attack complex.

Figure adapted from Ricklin D, et al. *Immunol Rev.* 2016;274:33–58. Liao DS, et al. *Ophthalmology.* 2020;127:186–195.

The DERBY and OAKS trials randomized intravitreal pegcetacoplan (C3 inhibitor) to sham injections either monthly or every other month (EOM).

Patients with GA secondary to AMD
~600 patients at ~200 sites globally in 2 studies (1258 enrollees total)

Randomized 2:2:1:1

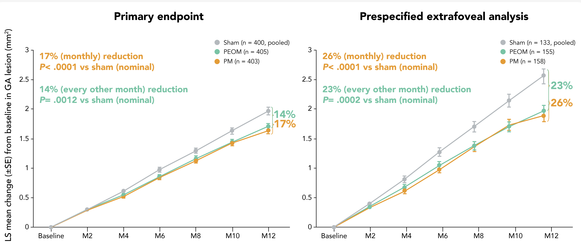
Pegcetacoplan 15 mg/0.1 mL monthly	Pegcetacoplan 15 mg/0.1 mL EOM	Sham monthly	Sham EOM

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)

Pegcetacoplan reduced lesion growth in analyses of both the primary endpoint AND prespecified analysis of extrafoveal lesions at 12 months.



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, OAKS, and FILLY (Phase 2 study) all show consistent efficacy of pegcetacoplan in treated study eyes versus untreated fellow eyes.

Combined Studies	PM (N= 419)	PEOM (N= 420)	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

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, however, *did not* meet the primary endpoint in DERBY. Pegcetacoplan demonstrated greater efficacy in patients with extrafoveal lesions at baseline, and has shown efficacy in treated study eyes versus untreated fellow eyes.

Overall, pegcetacoplan was well tolerated in patients with GA, with the majority of intraocular inflammation (IOI) cases being mild and most patients resuming treatment. New-onset investigator determined eAMD was experienced in 6.0% monthly and 4.1% EOM pegcetacoplan groups (combined), and 2.4% of sham groups (combined).