Efficacy and safety of intravitreal pegcetacoplan in geographic atrophy: results from the phase 3 OAKS and DERBY trials

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Purpose: Currently, no approved therapies exist to slow the progression of geographic atrophy (GA)

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

Patients with GA secondary to AMD
~600 patients at ~200 sites globally in 2 studies (1,258 enrollees total)

Randomised 2:2:1:1

Double-masked

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

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

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

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

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

GALE open-label extension study (3 years)

AMD=age-related macular degeneration; BCVA=best corrected visual acuity; EOM=every other month; FRI=functional reading independence; GA=geographic atrophy; LL=low luminance; NEI-VFQ=National Eye Institute Visual Function Questionnaire-25.

OAKS: Key demographics and baseline study eye characteristics

Characteristics		PM (N=202)	PEOM (N=205)	Sham Pooled (N=206)
Age, mean (SD)		78.8 (7.24)	78.1 (7.74)	78.6 (7.25)
Female, n (%)		125 (61.9%)	117 (57.1%)	133 (64.6%)
Male, n (%)		77 (38.1%)	88 (42.9%)	73 (35.4%)
Geographic region				
USA, 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, n (%)	<7.5 mm^2	101 (50.0%)	98 (47.8%)	104 (50.2%)
GA lesion location, n (%)	Extrafoveal	86 (42.6%)	74 (36.1%)	60 (29.0%)
GA lesion focality, n (%)	Unifocal	59 (29.2%)	62 (30.2%)	68 (32.9%)
Intermediate/large drusen, n (%)	>20	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)

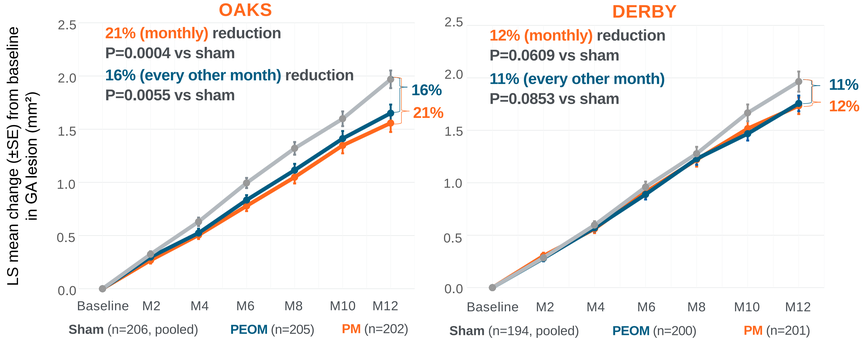
These analyses were performed on the modified intent-to-treat (mITT) population. The mITT population was defined as all randomised patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion area in the study eye.
ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; NL-BCVA=normal luminance best-corrected visual acuity; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; ROW=rest of world; SD=standard deviation.

DERBY: Key demographics and baseline study eye characteristics

Characteristics		PM (N=201)	PEOM (N=200)	Sham Pooled (N=194)
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 (36.19%)
Geographic region				
USA, n (%)		142 (70.6%)	122 (60.7%)	122 (62.6%)
ROW, n (%)		59 (29.4%)	78 (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, n (%)	<7.5 mm^2	99 (49.3%)	98 (48.8%)	95 (48.7%)
GA lesion location, n (%)	Extrafoveal	72 (35.8%)	81 (40.3%)	73 (37.4%)
GA lesion focality, n (%)	Unifocal	54 (26.9%)	53 (26.4%)	66 (33.8%)
Intermediate/large drusen, n (%)	>20	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 modified intent-to-treat (mITT) population. The mITT population was defined as all randomised 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; NL-BCVA=normal luminance best-corrected visual acuity; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; ROW=rest of world; SD=standard deviation.

Pegcetacoplan administered monthly (PM) and every other month (EOM) met the primary endpoint at 12 months in OAKS but not in DERBY

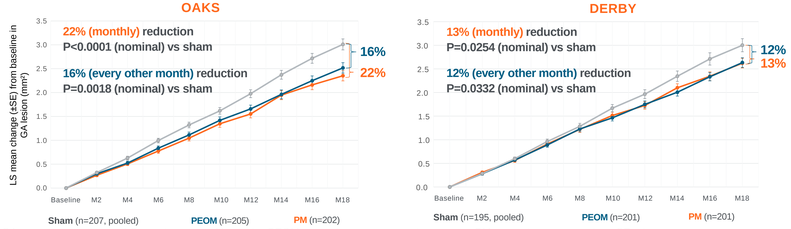


LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion area in the study eye. GA=geographic atrophy; LS=least squares; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan reduced lesion growth in a prespecified pooled analysis at 12 months

- Reductions were 16% (P=0.0001) and 14% (P=0.0014) in monthly and every-other-month (EOM) arms, respectively, vs sham

Pegcetacoplan further reduced lesion growth at 18 months



GA=geographic atrophy; LS=least squares; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan reduced lesion growth in a prespecified pooled analysis at 18 months

- Reductions were 17% (P<0.0001) and 15% (P=0.0002) in monthly and EOM arms, respectively, vs sham

Safety profile at 12 and 18 months

Safety profile at 12 months

Intraocular inflammation (IOI):

- 13 patients (1.5%) experienced 14 events of IOI
  - Four of these cases, including one case of non-infectious (culture negative) endophthalmitis, were reported in 2018 and linked to drug impurity; excluding these cases, the rate of IOI per patient over 12 months was 1.1%
- Rate of IOI per injection: 0.22%
- No cases of retinitis or vasculitis (occlusive or non-occlusive) were reported
- Majority of cases were mild, and 10/13 patients resumed investigational product administration, without subsequent recurrence of IOI

Infectious endophthalmitis:

- Two cases with culture positive for Gram-positive bacteria; one case with no culture results
- All patients treated with intravitreal antibiotics; one case also treated with pars plana vitrectomy
- Rate of infectious endophthalmitis per injection: 0.047%
- Rate of infectious endophthalmitis per patient over 12 months: 0.36%
- Rate of infectious endophthalmitis is consistent with other trials with intravitreal injections

Exudative AMD (eAMD):

- 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-vascular endothelial growth factor therapy per label

Safety profile at 18 months

- Over 18 months:
  - 21 events of IOI were observed in 18 patients. Rate of IOI per injection: 0.23%
  - 4 cases of infectious endophthalmitis. Rate per injection: 0.044% (9,145 total injections)
  - No cases of retinitis or vasculitis (occlusive or non-occlusive) were reported
- 9.5%, 6.2%, and 2.9% of patients in the combined PM, PEOM, and sham groups experienced new-onset investigator-determined eAMD

Conclusions

- OAKS is the first phase 3 trial in patients with GA to meet its primary endpoint, with positive trends also observed in the DERBY phase 3 trial
  - At 12 months, the OAKS study met the primary endpoint for monthly and EOM pegcetacoplan treatment
  - At 12 months, the DERBY study did not meet the primary endpoint for monthly and EOM pegcetacoplan
  - Administration of pegcetacoplan monthly and EOM reduced the growth of atrophic lesions at 18 months
    - In a prespecified pooled analysis, pegcetacoplan monthly and EOM significantly reduced lesion growth at 12 months versus sham
- Overall, monthly and EOM pegcetacoplan administration was well tolerated by patients with GA
- Results were consistent at 18 months with sustained reduction in lesion growth and a similar safety profile

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