# Long-Term Efficacy and Safety of Pegcetacoplan Over 36 Months: Results From 12 Months of the GALE Open-Label Extension Study

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*on behalf of OAKS, DERBY, and GALE Investigators*

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## Introduction

- Geographic atrophy (GA) is a progressive and irreversible advanced form of age-related macular degeneration (AMD)[1]
- More than 5 million people are affected by GA worldwide, with its incidence predicted to rise globally[1,2]
- GA is associated with worse quality of life, decreased physical functioning, and increased risk of clinical depression[1]

## Purpose

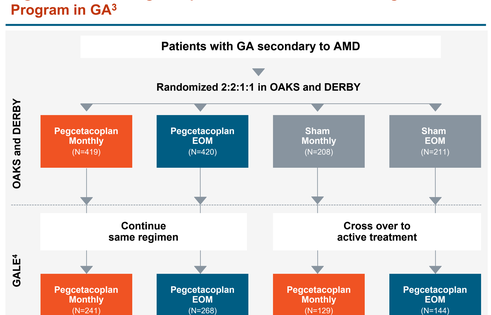
- To report the efficacy and safety of continuous intravitreal pegcetacoplan treatment in patients with GA over 36 months from GALE (NCT04770545), an open-label extension study of the phase 3 OAKS (NCT03525613) and DERBY (NCT03525600) trials

## Methods

### *Study Design*

- The GALE study is a 3-year open-label extension study following the 2-year OAKS and DERBY studies, allowing for a total of 5 years of continuous pegcetacoplan treatment (**Figure 1**)
  - Patients in the pegcetacoplan monthly (PM) and every other month (PEOM) arms in OAKS and DERBY continued the same treatment regimen, and patients in the sham arm crossed over to active treatment with pegcetacoplan based on their prior treatment interval
- Efficacy analysis: change in GA lesion area based on 12-month GALE data
  - 36-month continuous treatment with pegcetacoplan was compared with sham
    - Sham = actual sham (24 months OAKS and DERBY) + projected sham (12 months GALE)
- Safety data through 36 months
  - Exudative AMD, intraocular inflammation (IOI), ischemic optic neuropathy (ION)
- 83% of patients who completed OAKS and DERBY continued on to GALE

### Figure 1. GALE: Largest Open-Label Extension and Longest Clinical Program in GA[3]




**AMD,** age-related macular degeneration; **EOM,** every other month; **GA,** geographic atrophy.

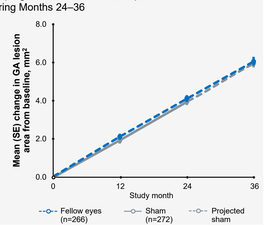
### *Validity of Projected Sham*

- Projected sham was estimated by calculating the average of the mean rate of change during each 6-month period of sham treatment
  - Validity of projected sham was corroborated both by known linear growth of lesion area from natural history studies[5] and from GA lesion growth rates in both the sham-treated eyes and untreated fellow eyes in OAKS and DERBY (**Figure 2**)
- The linear growth rates of sham-treated eyes and untreated fellow eyes were nearly identical at ~2 mm$^2$ per year
  - The consistent growth rates were reinforced by plotting the GA lesion growth rates of the pooled fellow eyes on top of overlayed on the sham-treated eyes and projected sham

### Figure 2. Linear GA Lesion Growth Rates of Sham-Treated and Untreated Fellow Eyes Corroborate Projected Sham Methodology

**Projected sham:** Expected rate of lesion progression if sham-treated patients remained on sham during Months 24–36

| Annual Mean Slope | Sham-Treated Eyes OAKS and DERBY (N=402) | Untreated Fellow Eyes GALE (N=266) |
|---|---|---|
| Months 0–12 | **1.98** | **2.04** |
| Months 12–24 | **2.02** | **1.98** |
| Months 24–36 | — | **1.94** |
| Mean | **2.00** | **1.99** |




**GA,** geographic atrophy; **SE,** standard error.

## Results

### *Patient Disposition*

- 92% of patients who enrolled in GALE completed the first year (**Table 1**)

### Table 1. GALE: Patient Disposition

| | PM to PM | PEOM to PEOM | SM to PM | SEOM to PEOM | Overall |
|---|---|---|---|---|---|
| Enrolled in GALE, n | 250 | 269 | 129 | 144 | 792 |
| Included in modified full analysis set, n | 241 | 267 | 129 | 143 | 780 |
| Excluded from modified full analysis set, n | | | | | |
| No injection received in GALE | 0 | 1 | 0 | 1 | 2 |
| Enrolled from study other than OAKS or DERBY[a] | 9 | 1 | 0 | 0 | 10 |
| Completed GALE through Month 36, n (%) | 234 (93.6) | 243 (90.7) | 115 (89.1) | 135 (94.4) | 727 (92.0) |
| Discontinued GALE prior to Month 36, n | | | | | |
| Consent withdrawal | 16 | 25 | 14 | 8 | 63 |
| Deaths | 4 | 14 | 6 | 2 | 26 |
| AE | 5 | 8 | 5 | 3 | 21 |
| Lost to follow-up | 3 | 3 | 3 | 2 | 11 |
| Physician's decision | 4 | 0 | 0 | 0 | 4 |
| | 0 | 0 | 0 | 1 | 1 |

**92% patient retention in first year of GALE**

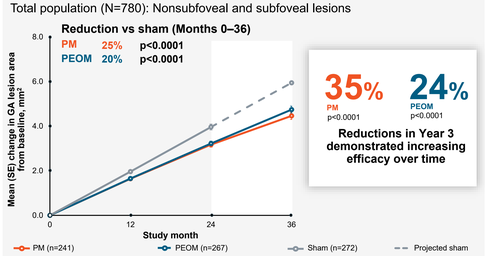
[a]Enrolled in GALE from Study 103, included in safety population.
**AE,** adverse event; **PEOM,** pegcetacoplan every other month; **PM,** pegcetacoplan monthly; **SEOM,** sham every other month; **SM,** sham monthly.

### *Lesion Growth and Tissue Preservation*

- With 36 months of continuous pegcetacoplan treatment, there were robust reductions in GA lesion growth in both PM and PEOM treatment arms (**Figure 3**)
  - Increasing efficacy was observed over time, with a 35% reduction in GA lesion growth rate with PM and 24% with PEOM from Months 24–36
  - Benefit with pegcetacoplan treatment was seen in both nonsubfoveal and subfoveal lesions

### Figure 3. Pegcetacoplan Showed Increasing Efficacy Over Time in an All-Comers[a] GA Population

Total population (N=780): Nonsubfoveal and subfoveal lesions

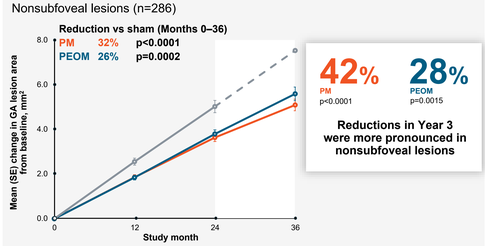



P-values are nominal. This piecewise linear slope analysis is based on a mixed-effects model evaluating mean rate of change from baseline to Month 36, with knots at Months 12 and 24 allowing for the slope to be linear in each 12-month segment. Projected sham was estimated from the mean rate of change in each 6-month period in Months 0–24. Modified full analysis set analysis: patients enrolled from OAKS/DERBY's ITT set who received ≥1 injection of pegcetacoplan in GALE.
[a]Population included patients with nonsubfoveal GA lesions and patients with subfoveal GA lesions.
**GA,** geographic atrophy; **ITT,** intent to treat; **PEOM,** pegcetacoplan every other month; **PM,** pegcetacoplan monthly; **SE,** standard error.

- In nonsubfoveal lesions, the reductions in GA lesion growth rate were even more pronounced as the nonsubfoveal lesions grew faster (**Figure 4**)
- Pegcetacoplan approximately tripled the amount of retinal tissue preserved at Year 3 vs Year 1 with both PM and PEOM dosing in nonsubfoveal lesions (**Figure 5**)
  - Over 36 months, the amount of retinal tissue preserved was 2.44 mm$^2$ with PM and 1.94 mm$^2$ with PEOM in nonsubfoveal lesions
  - This amount of retinal tissue preserved is approximately the size of the optic nerve head/optic disc area (approximately 2.1–2.8 mm$^2$ and varies by ethnicity)[6,7]

### Figure 4. Pegcetacoplan Reduced GA Lesion Growth in Nonsubfoveal Lesions

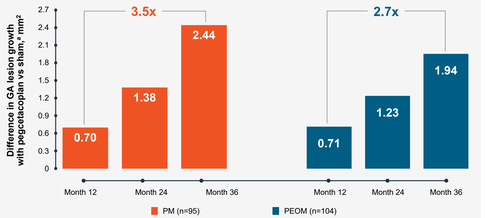
Nonsubfoveal lesions (n=286)




P-values are nominal. This piecewise linear slope analysis is based on a mixed-effects model evaluating mean rate of change from baseline to Month 36, with knots at Months 12 and 24 allowing for the slope to be linear in each 12-month segment. Projected sham was estimated from the mean rate of change in each 6-month period in Months 0–24. Modified **full analysis set** analysis: patients enrolled from OAKS/DERBY's ITT set who received ≥1 injection of pegcetacoplan in GALE.
**GA,** geographic atrophy; **ITT,** intent to treat; **PEOM,** pegcetacoplan every other month; **PM,** pegcetacoplan monthly; **SE,** standard error.

### Figure 5. Pegcetacoplan Treatment Approximately Tripled Retinal Tissue Preserved

Nonsubfoveal lesions (n=286)

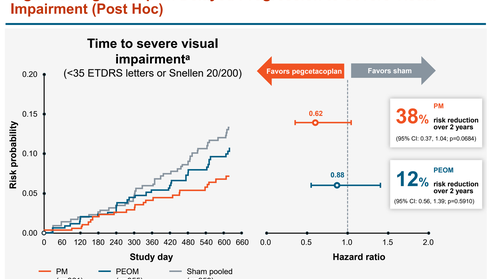



[a]Difference in GA lesion growth vs pooled sham up to Month 24 and vs projected sham at Month 36. Projected sham was estimated from the mean rate of change in each 6-month period in Months 0–24.
**GA,** geographic atrophy; **PEOM,** pegcetacoplan every other month; **PM,** pegcetacoplan monthly.

### *Visual Acuity*

- Treatment with PM and PEOM corresponded to a 38% and 12% reduction, respectively, for severe visual impairment over 2 years compared with sham (**Figure 6**)
  - Severe visual impairment defined as vision <35 Early Treatment Diabetic Retinopathy Study (ETDRS) letters,[8] or <20/200

### Figure 6. Pegcetacoplan Delayed Progression to Severe Visual Impairment (Post Hoc)




[a]Analysis based on 24-month OAKS and DERBY data. P-values are nominal. Hazard ratio estimated from Cox proportional hazards model including patients in the modified ITT population at-risk for the event with ≥1 post-baseline assessment.
**CI,** confidence interval; **ETDRS,** Early Treatment Diabetic Retinopathy Study; **ITT,** intent to treat; **PEOM,** pegcetacoplan every other month; **PM,** pegcetacoplan monthly.

### *Safety*

- Pegcetacoplan was well tolerated in the first 12 months of GALE (**Table 2**)
  - The safety profile of pegcetacoplan during GALE was consistent with the findings of the 24-month OAKS and DERBY studies[3]
- Rates of adverse events of interest from OAKS, DERBY, and GALE between Months 0–36 were:
  - Infectious endophthalmitis: ~1/3000 injections (0.03% per injection)
  - ION: ~1/2000 injections (0.05% per injection)
  - IOI: ~1/370 injections (0.27% per injection)
- Over 36 months, there were no study events of occlusive or non-occlusive retinitis or vasculitis

### Table 2. Safety Profile in First 12 Months of GALE Consistent With OAKS and DERBY

| GALE[a] Months 24–36 | PM to PM (n=250) | SM to PM (n=129) | PEOM to PEOM (n=268) | SEOM to PEOM (n=143) |
|---|---|---|---|---|
| **AEs in study eye reported in ≥2% of patients, %** | | | | |
| Ocular discomfort | 3.6 | 6.2 | 2.6 | 7.0 |
| Exudative AMD[b] | 8.8 | 6.2 | 2.6 | 2.8 |
| Cataract | 5.2 | 3.9 | 1.9 | 3.5 |
| Vitreous floaters | 4.4 | 10.1 | 2.2 | 5.6 |
| Conjunctival hemorrhage | 3.2 | 9.3 | 2.6 | 4.2 |
| Retinal hemorrhage | 3.2 | 2.3 | 2.2 | 1.4 |
| Intraocular pressure increased | 4.8 | 3.9 | 5.2 | 1.4 |
| **AEs of interest in study eye, patients (%)** | | | | |
| Infectious endophthalmitis | 0 | 1 (0.8) | 0 | 0 |
| IOI[b] | 6 (2.4) | 5 (3.9) | 2 (0.7) | 2 (1.4) |
| ION | 1 (0.4) | 0 | 0 | 0 |

[a]Safety population, consisting of all enrolled patients who received ≥1 pegcetacoplan injection and analyzed according to the actual treatment received.
[b]The following terms were combined: ocular discomfort included eye pain, eye irritation, ocular discomfort; exudative AMD included exudative AMD, choroidal neovascularization.
**AE,** adverse event; **AMD,** age-related macular degeneration; **IOI,** intraocular inflammation; **ION,** ischemic optic neuropathy; **PEOM,** pegcetacoplan every other month; **PM,** pegcetacoplan monthly; **SEOM,** sham every other month; **SM,** sham monthly.

## Conclusion

- Pegcetacoplan demonstrated increasing efficacy over time through 36 months with as few as 6 injections per year
  - In nonsubfoveal lesions, there was a 42% reduction in GA lesion growth rate with PM during Months 24–36
- Progression to severe visual impairment was delayed with pegcetacoplan treatment with up to a 38% risk reduction over 2 years
  - This delay in progression to severe visual impairment supports the trend in functional benefit with pegcetacoplan treatment
- The safety profile of pegcetacoplan during GALE was consistent with the findings of the 24-month OAKS and DERBY studies
  - No new cases of occlusive or non-occlusive retinitis or vasculitis were observed

## References

**1.** Bakri S, et al. *J Manag Care Spec Pharm.* 2023;29(5):S1–S10. **2.** Fleckenstein M, et al. *Ophthalmology.* 2018;125(3):369–390. **3.** Heier JS, et al. *Lancet.* 2023;402:1434–1448. **4.** ClinicalTrials.gov. Accessed April 30, 2024. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04770545. **5.** Sunness JS, et al. *Ophthalmology.* 2007;114:271–277. **6.** Jonas JB, et al. *Surv Ophthalmol.* 1999;43(4):293–320. **7.** Nousome D, et al. *Ophthalmology.* 2021;128(7):1005–1015. **8.** Pan American Health Organization. Accessed April 30, 2024. Available from: https://www.paho.org/en/topics/visual-health.

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