Pegcetacoplan GA—Visual Function Outcomes in the OAKS, DERBY and GALE Studies

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SYFOVRE intravitreal injection for ophthalmic use, is a complement inhibitor indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).[1]

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SUMMARY

- In the completed Phase 3 OAKS and DERBY studies and the ongoing Phase 3b open-label, extension GALE study, pegcetacoplan reduced GA lesion growth with increasing efficacy over time in both pegcetacoplan monthly (PM) and every other month (PEOM) arms compared with pooled sham/projected sham through Month 36.[2]
  - In OAKS and DERBY at 24 months, no notable differences in key secondary visual endpoints were observed across treatment arms.[2]
- In OAKS and DERBY combined, a post-hoc subgroup analysis was conducted to estimate the impact of pegcetacoplan treatment on the time to severe visual impairment [<35 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen 20/200)].[5]
  - Through Month 24, treatment with PM and PEOM was shown to reduce the risk of progression to severe visual impairment by 38% and 12% vs. sham pooled, respectively.[5]
- In OAKS, a post-hoc analysis of microperimetry endpoints in the junctional zone (≤250 µm) was conducted at 24 months. In the total population, pegcetacoplan maintained retinal sensitivity and reduced the development of new scotomatous points.[6]
- In OAKS, a post-hoc central macular light sensitivity analysis was conducted in patients that had at least 1 of the 4 and 16 central loci with light sensitivity on microperimetry.[6]
  - Over 24 months, treatment with PM and PEOM was shown to reduce the risk of progression to absolute scotoma in the 4 central macular loci by 34% and 36%, respectively. Similar results were observed in the 16 central loci analysis.[5]
- In OAKS and GALE, a prespecified analysis of the number of new scotomatous points on microperimetry was conducted through Month 36.[5,8]
  - At Month 36, the PM arm showed fewer new scotomatous points compared to sham crossover (p=0.0156). A similar trend towards fewer new scotomatous points was observed with PEOM (p=0.1233).[5,8]
- In GALE, a post-hoc, covariate adjusted subgroup analysis was conducted to estimate the impact of pegcetacoplan on change from baseline in BCVA [measured in ETDRS letters], based on distance of the GA lesion from the foveal center.[9]
  - At Month 30, pegcetacoplan treatment was associated with a loss of 8.4 fewer ETDRS letters vs. sham (sham patients were on treatment Months 24-30) in GA lesions ≥250 µm from the foveal center.[9]

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- Safety data was collected from over 18,000 pegcetacoplan injections in over 1,100 patients across the 3 studies. The safety profile in GALE at Month 36 was similar to that observed in the 24-month pivotal Phase 3 OAKS and DERBY studies.[11-13]

STUDY DESIGN

Phase 3 Studies: OAKS & DERBY

OAKS (NCT03525613) and DERBY (NCT03525600) were two 24-month, multicenter, randomized, double-masked, sham-controlled Phase 3 studies that compared the efficacy and safety of intravitreal (IVT) pegcetacoplan with sham injections in patients with GA.[2]

Patients in the OAKS (N=637) and DERBY (N=621) studies were randomized 2:2:1:1 to treatment with pegcetacoplan monthly (PM) or every other month (PEOM) IVT injection (15 mg/0.1 mL) or monthly or every other month sham injections. Patients in OAKS and DERBY continued on masked treatment for 24 months. The primary endpoint of the studies was the change from baseline to Month 12 in total area (mm^2) of GA lesions as measured by fundus autofluorescence (FAF; prespecified statistical significance level of $p<0.05$). Key secondary visual function endpoints were analyzed at Month 24 in the modified intent-to-treat (mITT) population. Microperimetry was measured in OAKS only.[2]

Phase 3b Long-term Extension Study: GALE

GALE (NCT04770545) is an ongoing Phase 3, open-label, multicenter, extension study to evaluate the long-term safety and efficacy of IVT pegcetacoplan in patients with GA.[3]

A total of 792 patients enrolled in the GALE study, of which 780 completed treatment at Month 24 of the antecedent OAKS and DERBY studies, received ≥1 pegcetacoplan injection in the GALE study, and were included in the modified full analysis set. The safety population included an additional 10 patients from Study APL2-103 (Phase 1b Safety Study; NCT03777332), for a total of 790 patients.[3]

Those who received pegcetacoplan (15 mg/0.1 mL) in OAKS and DERBY continued to receive pegcetacoplan at the same frequency in GALE; those who received sham in OAKS and DERBY transitioned to receiving pegcetacoplan in GALE at the same interval. The primary endpoint of the study is to evaluate the incidence and severity of ocular and systemic adverse events up to 36 months. Key secondary visual function endpoints include change from baseline in normal-luminance best-corrected visual acuity (NL-BCVA) score and low-luminance (LL)-BCVA at 12, 24, and 36 months.[3] Microperimetry was performed only in OAKS patients and OAKS patients who continued into GALE.[4]

CLINICAL DATA

Secondary Visual Function Endpoints in OAKS & DERBY at 24 Months

In OAKS and DERBY at Month 24, no notable differences were observed across treatment arms on key secondary visual function endpoints: BCVA, maximum reading speed, Functional Reading Independence index, or microperimetry (mean threshold sensitivity, measured in OAKS only).[2]

Post-hoc Time-to-Event Analysis: Progression to Severe Visual Impairment in OAKS & DERBY Combined

A post-hoc subgroup analysis in patients without severe visual impairment at baseline (BCVA ≥20/200) in OAKS and DERBY combined was conducted to estimate the impact of pegcetacoplan treatment on the time to severe visual impairment. Severe visual impairment was defined as the first time a patient

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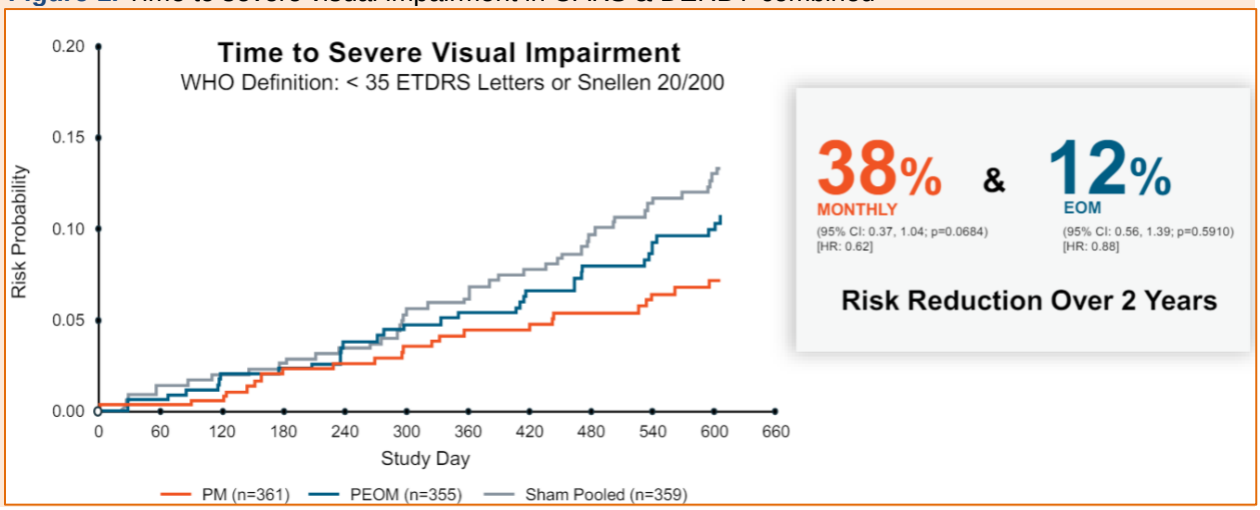
experienced vision worse than 35 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen 20/200) sustained for at least 4 months post-baseline without later recovery to ≥40 letters (Snellen 20/160) at a subsequent visit. Through Month 24, treatment with PM and PEOM reduced the risk of progression to severe visual impairment by 38% (hazard ratio [95% CI]: 0.62 [0.37, 1.04]) and 12% (hazard ratio [95% CI]: 0.88 [0.56, 1.39]) vs. sham pooled, respectively **(Figure 1)**.[5]

Figure 1. Time to severe visual impairment in OAKS & DERBY combined[5]



All p-values are nominal. Microperimetry only performed in OAKS. Hazard ratio estimated from Cox Proportional Hazards model including patients in the mITT population at-risk for the event with at least one post-baseline assessment. Model includes Treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline presence of choroidal neovascularization in the fellow eye (Yes or No) + baseline number of central 16 scotomatous points. CI=confidence interval; ETDRS=Early Treatment Diabetic Retinopathy Study; HR=hazard ratio; mITT=modified intent-to-treat; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; WHO=World Health Organization.

Post-hoc Microperimetry Analysis of the Junctional Zone in the OAKS Study Over 24 Months

A post-hoc analysis of microperimetry endpoints was conducted in the OAKS study at 24 months to assess potential treatment effects of pegcetacoplan on photoreceptor function in the junctional zone, defined as ±250 µm from the GA lesion border at baseline. The mean examination time for microperimetry was 8.8 minutes. Correlation of perilesional sensitivity with change in GA lesion area over time suggests that the junctional zone encompasses the area of greatest disease activity and therefore is at highest risk for changes in mean threshold sensitivity and number of scotomatous points.[6] The average linear growth of GA lesions is approximately 100-150 µm per year.[7]

Microperimetry Analysis of the Junctional Zone–OAKS Total Population Over 24 Months

In the total population, a decreased loss of mean threshold sensitivity within the junctional zone was observed in both the PM (10%; *p*=0.0650) and PEOM (12%; *p*=0.0202) arms vs. the pooled sham arm. Between Months 18-24, a 43% and 46% difference in mean threshold sensitivity was demonstrated in both PM and PEOM arms, respectively. Fewer new scotomatous points were detected in the PM (10%; *p*=0.1444) and PEOM (16%; *p*=0.0140) arms. Between Months 18-24, a 18% and 41% reduction in the number of new scotomatous points was observed in both PM and PEOM arms, respectively **(Figure 2)**.[6]

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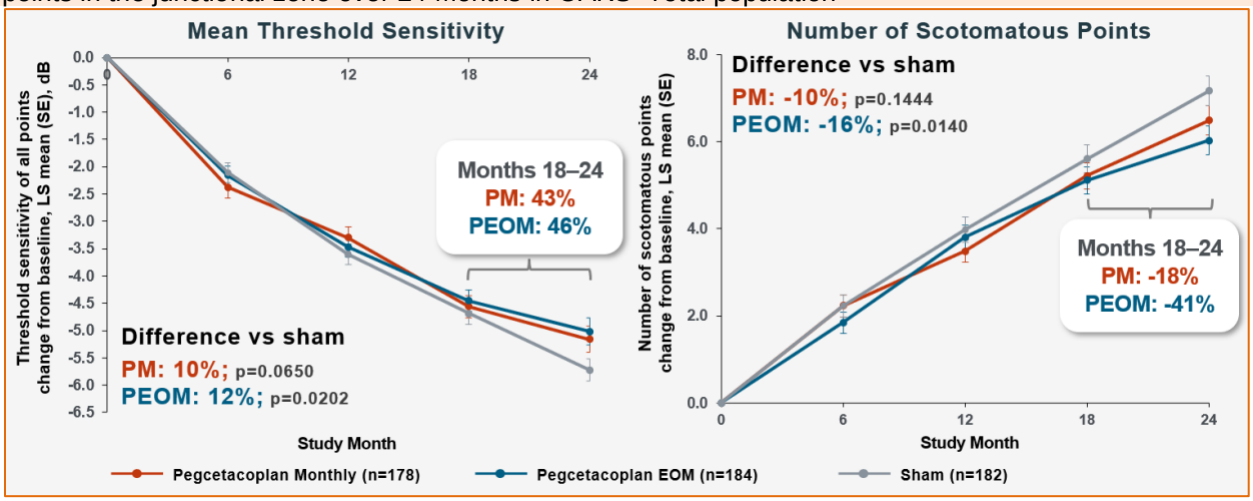
Figure 2. Microperimetry Analysis of change in mean threshold sensitivity and number of scotomatous points in the junctional zone over 24 Months in OAKS–Total population[6]



All p-values are nominal. LS means estimated from an MMRM. Patients in the mITT population who had a baseline and ≥1 post-baseline value for junctional zone mean threshold sensitivity or junctional zone number of scotomatous points were included in the analysis. Junctional zone was defined as -250 µm inside baseline atrophy border to +250 µm outside atrophy border.
dB=decibel; EOM=every other month; LS=least squares; mITT=modified intent-to-treat; MMRM=mixed-effects model for repeated measures; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Post-hoc Central Macular Light Sensitivity Analysis in the OAKS Study Over 24 Months

Maintaining central macular light sensitivity is crucial for macular functionality and visual function. In the OAKS study, a central macular light sensitivity analysis was conducted in patients with light sensitivity in at least one of the 4 central loci on microperimetry (10-2 Macular Integrity Assessment [MAIA] grid). Measurements were taken at baseline and every 6 months thereafter and recorded in a time-to-event analysis across treatment arms where the event was defined as onset of absolute scotomata at all 4 foveal loci.[6]

Central 4 Macular Loci

Over 24 months, PM and PEOM was shown to reduce the risk of progression to absolute scotoma (or loss of sensitivity) in the 4 central macular points which are equivalent to the central subfield by 34% (hazard ratio [95% CI]: 0.66 [0.46, 0.96]) and 36% (hazard ratio [95% CI]: 0.64 [0.44, 0.92]), respectively.[5]

In the OAKS study at baseline, patients with a higher number of scotomatous points in the central 4 loci corresponded to a lower baseline BCVA score **(Figure 3)**.[6]

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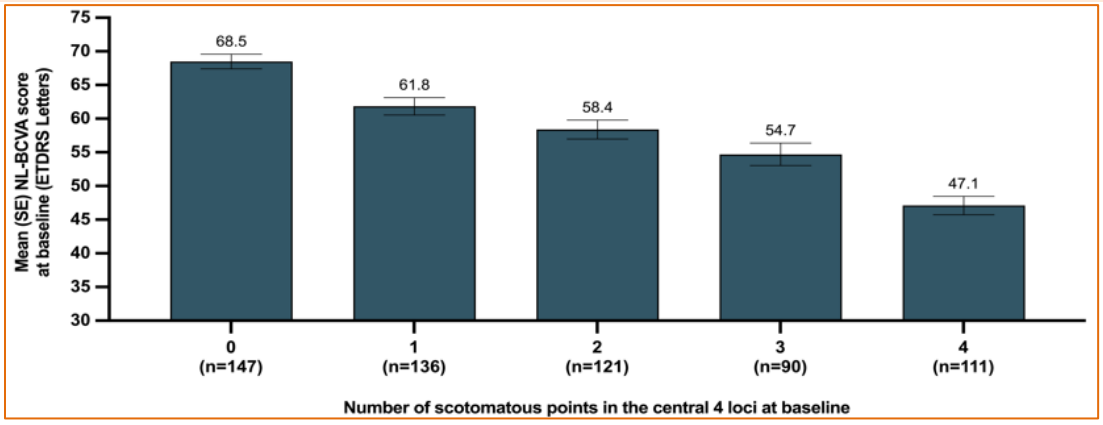
Figure 3. NL-BCVA score (ETDRS letters) associated with the number of scotomatous points in the central 4 loci at baseline in OAKS[6]



Model includes Treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline presence of choroidal neovascularization in the fellow eye (Yes or No) + baseline number of central 4 scotomatous points.
NL-BCVA=normal luminance best-corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy

At Month 24, patients who experienced a loss of all 4 central loci, resulting in absolute scotoma (n=149), lost an average of 11.7 ETDRS letters vs. baseline, whereas patients who retained sensitivity in at least one of the 4 points (n=183), lost an average of 4.9 ETDRS letters vs. baseline **(Table 1)**.[5]

Table 1. Loss of central 4 loci and associated BCVA change from baseline to Month 24 in OAKS[5]

BCVA Change from Baseline to Month 24	
Patient Loci Status at Month 24	ETDRS Letters (SD)
Scotoma at **all 4** central loci [n=149]	**-11.7** (17.33)
Scotoma at **< 4** central loci [n=183]	**-4.9** (11.16)

Model includes Treatment + baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) + baseline presence of choroidal neovascularization in the fellow eye (Yes or No) + baseline number of central 4 scotomatous points.
BCVA=best-corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; SD=standard deviation.

Central 16 Macular Loci

The same analysis was repeated for the central visual field of 16 macular points. Over 24 months, a 43% (hazard ratio [95% CI]: 0.57 [0.33, 0.96]) and 48% (hazard ratio [95% CI]: 0.52 [0.32, 0.85]) reduction in the risk of progression to absolute scotoma at the central 16 macular points (which cover the entire fovea), was observed with treatment with PM and PEOM, respectively.[5]

At Month 24, patients who experienced a loss of all 16 central loci resulting in absolute scotoma (n=76), lost an average of 12.7 ETDRS letters vs. baseline, whereas patients who retained sensitivity in at least one of the 16 points (n=316) lost an average of 6.3 ETDRS letters vs. baseline.[5]

Prespecified Microperimetry Endpoint: Number of Scotomatous Points in the OAKS & GALE Studies Over 36 Months

A prespecified analysis of the number of new scotomatous points on microperimetry was conducted through Month 36. Microperimetry was measured only in OAKS patients and therefore, only OAKS

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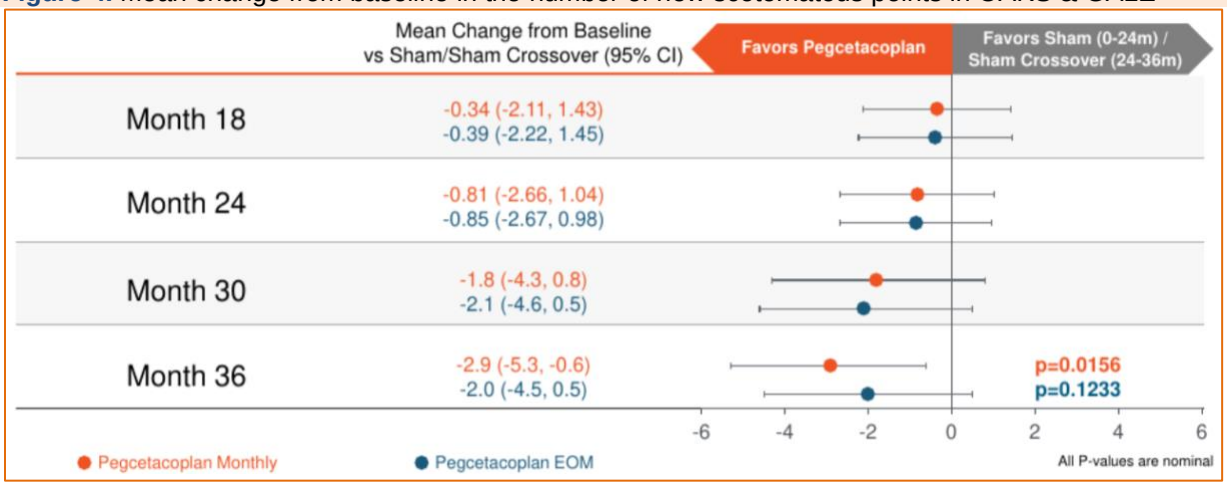
patients who continued into GALE were included in this analysis.[4] In OAKS (Months 0-24), the mean change from baseline of new scotomatous points in PM and PEOM were compared to pooled sham. At Month 24, there was no statistically significant difference observed between treatment arms and sham. In GALE (Months 24-36), the mean change from baseline of new scotomatous points in PM and PEOM were compared to the sham crossover arm. At Month 36, the PM arm showed fewer new scotomatous points compared to sham crossover (*p*=0.0156). A similar trend towards fewer new scotomatous points was observed with PEOM **(Figure 4)**.[5,8]

Figure 4. Mean change from baseline in the number of new scotomatous points in OAKS & GALE[5,8]



P-values are nominal. Sham refers to the sham pooled group over Months 0-24 and the sham crossover group over Months 24-36. LS means estimated from mixed models for repeated measures analyses. Included in this analysis were patients in the modified intent-to-treat population who had a baseline and ≥1 post-baseline value through the corresponding visit for overall number of scotomatous points (Months 18/24: n=552, Months 30/36: n=556). CI=confidence interval; LS=least-squares.

Post-hoc Visual Function Subgroup Analysis: Baseline Distance from Foveal Center in the GALE Study Over 30 Months

A post-hoc subgroup analysis in patients with GA lesions ≥250 µm or <250 µm from the foveal center was conducted to estimate the impact of pegcetacoplan treatment on change from baseline in BCVA, measured in ETDRS letters, across pooled data from the OAKS, DERBY, and GALE studies. Artificial intelligence-based automated segmentation of retinal pigment epithelium (RPE) loss data was collected from patients with Heidelberg Spectralis optical coherence tomography (OCT) images. Covariates for adjustment were prespecified *a priori* based on clinical rationale. These included patient demographics, baseline study eye characteristics (including foveal occupancy, the proportion of the central 3 mm foveal region occupied by the GA lesion), and fellow eye characteristics.[9]

Observations from baseline data from the OAKS and DERBY studies, together with literature reports, demonstrated the correlation between foveal occupancy and visual function. A limitation of this analysis was that RPE loss data was unavailable for patients with Cirrus (Zeiss) images. However, baseline characteristics of patients with Heidelberg Spectralis and Cirrus OCT images were similar.[10]

BCVA Change from Baseline to Month 30 in Lesions ≥250 µm From the Foveal Center

In the ongoing GALE study, continued BCVA benefits were observed after 30 months of continuous pegcetacoplan treatment. At Month 30, the analysis demonstrated that pegcetacoplan treatment was associated with loss of 8.4 fewer ETDRS letters vs. sham (sham patients were on treatment Months 24 to 30) in patients with GA lesions located ≥250 µm from the foveal center **(Figure 5)**.[9]

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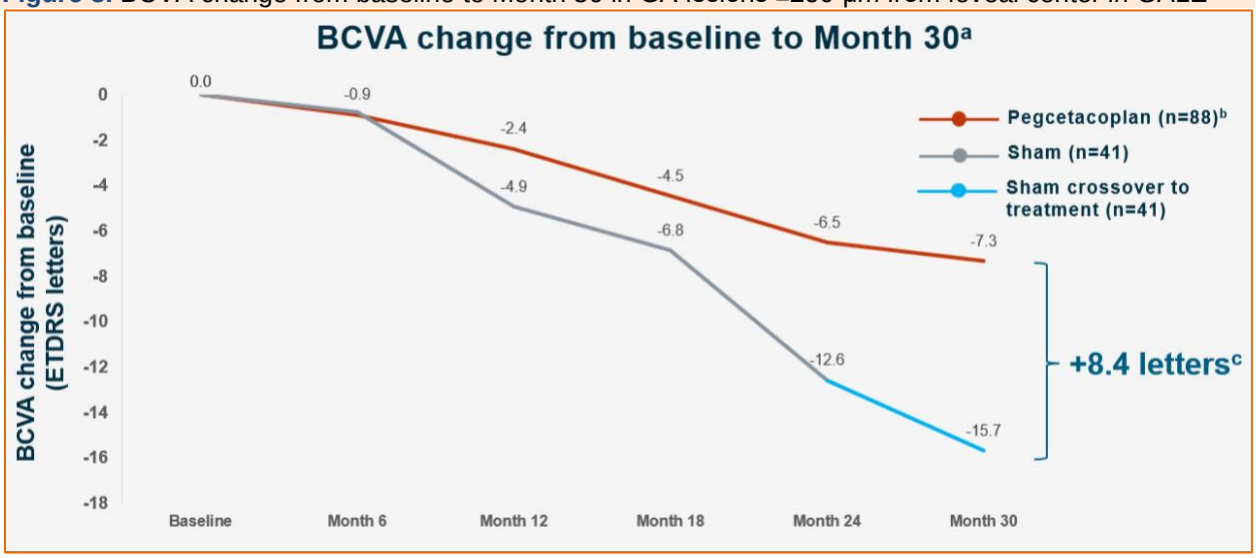
Figure 5. BCVA change from baseline to Month 30 in GA lesions ≥250 µm from foveal center in GALE[9]



[a] Includes patients in the sample with non-missing baseline measurements of central macular occupancy in regions 1–5 and lesion distance from fovea center who continued in the GALE study. Adjusted estimates from the model calculated among patients with BCVA measurements at each time point and thus samples vary across outcomes shown with no imputation for missing data. [b] The sample size reflects patients with available assessments between Months 24 and 30. [c] Adjusted difference, mean.
BCVA=best-corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study.

Safety Data Over 36 Months

Safety data was collected from over 18,000 pegcetacoplan injections in over 1,100 patients across 3 studies (OAKS, DERBY, and through the first 12 months of GALE). The safety profile in GALE at Month 36 was similar to that observed in the 24-month pivotal OAKS and DERBY studies.[11]

Ocular adverse events of interest in the combined OAKS and DERBY studies at Month 24 and the first 12 months of the GALE study are presented below in **Table 2**.[11-13]

Table 2. Ocular events of interest in the study eye in the combined OAKS & DERBY studies through Month 24 and in GALE from Months 24-36[11-13]

	OAKS & DERBY Combined Months 0-24			GALE Months 24-36			
AEs in the study eye, n (%)	PM (N=419)	PEOM (N=420)	Sham Pooled (N=417)	PM to PM (N=250)	SM to PM (N=129)	PEOM to PEOM (N=268)	SEOM to PEOM (N=143)
Infectious endophthalmitis	2 (0.5%)	2 (0.5%)	0	0	1 (0.8%)	0	0
IOI[a]	16 (3.8%)	9 (2.1%)	1 (0.2%)	6 (2.4%)	5 (3.9%)	2 (0.7%)	2 (1.4%)
ION	7 (1.7%)	1 (0.2%)	0	1 (0.4%)	0	0	0
	PM (N=419)	PEOM (N=419)[b]	Sham Pooled (N=417)	PM to PM (N=250)	SM to PM (N=129)	PEOM to PEOM (N=268)	SEOM to PEOM (N=143)
eAMD[c]	51 (12.2%)	28 (6.7%)	13 (3.1%)	7.9%	5.6%	2.0%	2.9%

[a] IOI included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare
[b] Number of patients at risk for new-onset eAMD in PEOM arms from combined OAKS and DERBY studies was 419
[c] Exudative age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization.
IOI=intraocular inflammation; ION=ischemic optic neuropathy; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SM=sham monthly; SEOM=sham every other month.

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Over 36 months in OAKS, DERBY, and GALE combined, the rate of infectious endophthalmitis in pegcetacoplan-treated patients was 0.03% per injection (~1 per 3,600 injections). The rate of IOI in pegcetacoplan-treated patients in OAKS, DERBY, and GALE combined was 0.26% per injection. This rate excludes 4 cases reported in 2018 that were attributed to drug impurity, one of which was an event of non-infectious (culture-negative) endophthalmitis. The rate of IOI including these cases was 0.28% per injection. No cases of occlusive or non-occlusive vasculitis or retinitis were reported. The rate of ION in pegcetacoplan-treated patients from OAKS, DERBY, and GALE combined was 0.05% (~1/2000 injections).[11]

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