Assessment of geographic atrophy progression in the phase 3 OAKS and DERBY trials

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Phase 3 OAKS and DERBY trials: Design and key criteria

Key inclusion criteria
- Age ≥60 years
- BCVA ≥24 letters ETDRS (20/320 Snellen equivalent)
- GA lesion requirements:
  - Total size: ≥2.5 and ≤17.5 mm²; if multifocal, at least one focal lesion must be ≥1.25 mm² (0.5 DA)
  - Presence of perilesional hyperautofluorescence
  - GA lesions with or without subfoveal involvement allowed

Key exclusion criteria
- GA secondary to a condition other than AMD, such as Stargardt disease, in either eye
- CNV in the study eye (active or history of), including presence of RPE tear (assessed by reading center)

Patients with GA secondary to AMD
1258 patients at 232 sites combined

Randomized 2:2:1:1

Pegcetacoplan monthly (N=419)
Pegcetacoplan EOM (N=420)
Sham monthly (N=208)
Sham EOM (N=211)

12-month primary endpoint
Change in total GA lesion area on FAF

- BCVA
- LLVA
- Reading speed
- NEI VFQ-25
- FRI Index score
- Microperimetry (OAKS)
- Lesion growth

24-month secondary endpoint

- GA=geographic atrophy; LL=low luminance; NEI-VFQ=National Eye Institute Visual Function Questionnaire; RPE=retinal pigment epithelium.

3-year open-label extension study

OAKS, DERBY, GALE CT.gov identifiers: NCT03525613, NCT03525600, NCT04770545, respectively. *Key secondary endpoints. AMD=age-related macular degeneration; BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; DA=disc area; EOM=every other month; ETDRS=Early Treatment Diabetic Retinopathy Study; FAF=fundus autofluorescence; FRI=Functional Reading Independence; GA=geographic atrophy; LL=low luminance; NEI-VFQ=National Eye Institute Visual Function Questionnaire; RPE=retinal pigment epithelium.
MRRM analysis (primary)

Reduction vs Sham
PM: 21%; p<0.0001
PEOM: 17%; p<0.0001

Piecewise linear slope analysis (post hoc)

Reduction vs Sham
PM: 20%; p<0.0001
PEOM: 17%; p<0.0001

Analysis performed on mITT population, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 postbaseline study eye GA lesion area value. Includes 1 patient in each of OAKS-Sham, DERBY-Pegcetacoplan EOM, and DERBY-Sham groups and had their first postbaseline GA lesion assessment after month 12. OAKS, NCT03525613; DERBY, NCT03525600. EOM, every other month; GA, geographic atrophy; LS, least squares; mITT, modified intent-to-treat; PM, pegcetacoplan monthly; PEOM, pegcetacoplan every-other-month.
Percent reductions vs sham pooled between Month 0 and Month 24 were estimated from a piecewise linear slope model with 6-month segments. GA=geographic atrophy; LS=least square; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Treatment effect on GA lesion growth across subgroups

Subgroup (baseline) | Favors pegcetacoplan | Favors sham | N PM/Sham | Difference in Treatment effect (nominal p-value)
---|---|---|---|---
GA lesion area ≥7.5 mm² | | | 203/202 | <0.0001
GA lesion area <7.5 mm² | | | 199/198 | 0.0030
BCVA ≥60 letters | | | 230/201 | <0.0001
BCVA <60 letters | | | 172/199 | 0.0007
Unifocal GA | | | 112/133 | <0.0001
Multifocal GA | | | 290/267 | <0.0001
Subfoveal lesion | | | 244/269 | <0.0001
Nonsubfoveal lesion | | | 158/131 | <0.0001
Unilateral GA | | | 71/85 | 0.0005
Bilateral GA | | | 331/315 | <0.0001
Female | | | 242/255 | <0.0001
Male | | | 160/145 | 0.0002

LS mean treatment difference, mm² (95% CI)

CI=confidence interval; ETDRS=Early Treatment of Diabetic Retinopathy Study; GA=geographic atrophy; LS=least square; BCVA=best corrected visual acuity; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.
OAKS and DERBY combined
Adverse events of interest at 24 months

<table>
<thead>
<tr>
<th>EXUDATIVE AMD*</th>
<th>OPTIC ISCHAEMIC NEUROPATHY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAEs</td>
</tr>
<tr>
<td>PM (n=419)</td>
<td>3</td>
</tr>
<tr>
<td>PEOM (n=420)</td>
<td>0</td>
</tr>
<tr>
<td>Sham (n=417)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INTRAOCULAR INFLAMMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 cases out of 11,736 pegcetacoplan injections</td>
</tr>
<tr>
<td>0.24% per injection</td>
</tr>
</tbody>
</table>

• All cases were evaluated by neuro-ophthalmologists
• All patients with OIN had discs at risk and multiple systemic risk factors

*Exudative AMD includes adverse events reported by the investigator as choroidal neovascularization or neovascular AMD. AEs=adverse events; AMD=age-related macular degeneration; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SAEs=serious adverse events.
Post hoc analysis of OAKS and DERBY: Quartile analysis of GA lesion growth over 24 months

GA=geographic atrophy; Q1=quartile 1; Q2=quartile 2; Q3=quartile 3; Q4=quartile 4.

Is pegcetacoplan treatment associated with a shift in distribution of patients into slower progressing quartiles?
Post hoc analysis: Methods and quartile definitions

GA progression measured by change in lesion area (mm$^2$) from baseline to Month 24

- GA progression by quartiles of growth assessed in the overall patient population
- Patients needed to have a Month 24 lesion growth measurement to be included in the analysis
- Total n=1000; 250 per quartile

<table>
<thead>
<tr>
<th>Lesion growth quartiles</th>
<th>Growth over 2 years (mm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1 slowest progressors</td>
<td>≤2.08</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>&gt;2.08–≤3.13</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>&gt;3.13–≤4.53</td>
</tr>
<tr>
<td>Quartile 4 fastest progressors</td>
<td>&gt;4.53</td>
</tr>
</tbody>
</table>

GA=geographic atrophy.
Distribution of patients by study arm across quartiles reflects efficacy of pegcetacoplan at 24 months

**OAKS**

- **PM difference vs sham in slow progressors**: 67% ↑
- **PM difference vs sham in fast progressors**: 58% ↓

**DERBY**

- **PM difference vs sham in slow progressors**: 52% ↑
- **PM difference vs sham in fast progressors**: 38% ↓

PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; Q=quartile.
Distribution of patients by study arm across quartiles reflects efficacy of pegcetacoplan at 24 months

**OAKS and DERBY combined**

- **PM difference vs sham in slow progressors**
  - Q1 slow progressors: n=86
  - Q4 fast progressors: n=105

- **PM difference vs sham in fast progressors**
  - Q1 slow progressors: n=85
  - Q4 fast progressors: n=65

**PM**
- 59% ↑

**PEOM**
- 48% ↓

PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; Q=quartile.
Example of GA lesion growth of 1.15 mm² on FAF

FAF=fundus autofluorescence.
Amount of retina tissue preserved (mm²) with pegcetacoplan treatment

OAKS and DERBY combined

Difference in LS mean GA lesion size vs sham pooled (mm²)

<table>
<thead>
<tr>
<th>Month</th>
<th>Pegcetacoplan monthly (n=403)</th>
<th>Pegcetacoplan EOM (n=406)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.14</td>
<td>0.12</td>
</tr>
<tr>
<td>12</td>
<td>0.33</td>
<td>0.27</td>
</tr>
<tr>
<td>18</td>
<td>0.52</td>
<td>0.43</td>
</tr>
<tr>
<td>24</td>
<td>0.82</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Difference vs sham in GA lesion area at 24 months

- PM: 0.82 mm²
- PEOM: 0.69 mm²

Prespecified MMRM

Absolute cumulative difference in lesion size vs pooled sham at Month 6, Month 12, Month 18, and Month 24 (‘preserved area’) from main MMRM analysis. Performed on mITT population, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 postbaseline study eye GA lesion area value. Includes 1 patient in each of OAKS-Sham, DERBY-Pegcetacoplan EOM, and DERBY-Sham groups who had their first postbaseline GA lesion assessment after month 12. OAKS, NCT03525613; DERBY, NCT03525600. EOM, every other month; GA, geographic atrophy; LS, least squares; mITT, modified intent-to-treat.
Retinal tissue and RPE cells preserved* with pegcetacoplan

<table>
<thead>
<tr>
<th>Pegcetacoplan monthly ( (n=403) )</th>
<th>Pegcetacoplan EOM ( (n=406) )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6-month intervals</strong></td>
<td><strong>Retinal tissue saved (mm(^2))</strong></td>
</tr>
<tr>
<td>0–6 months</td>
<td>0.14</td>
</tr>
<tr>
<td>6–12 months</td>
<td>0.20</td>
</tr>
<tr>
<td>12–18 months</td>
<td>0.19</td>
</tr>
<tr>
<td>18–24 months</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Total over 24M(^a)</strong></td>
<td><strong>0.82</strong></td>
</tr>
</tbody>
</table>

*Estimated based on macular RPE density\(^1\) range of 5082 cells/mm\(^2\) to 7728 cells/mm\(^2\)

\(^a\)Numbers may differ slightly from total of 6-month intervals due to rounding.

OAKS and DERBY combined / prespecified analysis

Reductions in GA lesion growth by lesion location

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.

EOM=every other month; GA=geographic atrophy; LS=least square; SE=standard error.
OAKS and DERBY combined
Cumulative preservation of retinal tissue in nonsubfoveal lesions

Absolute cumulative difference in lesion size vs pooled sham at Month 6, Month 12, Month 18, and Month 24 (‘preserved area’) from main MMRM analysis of mITT population. Fovea size calculated from average diameter of 1.5 mm per Kolb et al., *The Architecture of the Human Fovea*. EOM=every other month; GA=geographic atrophy; NSF=nonsubfoveal; PM=pegcetacoplan monthly. mITT=modified intent-to-treat; MMRM=mixed-effects model for repeated measures.

Difference in LS mean GA lesion size vs sham pooled (mm²)

- Pegcetacoplan monthly (n=158)
- Pegcetacoplan EOM (n=155)

Month 6: 0.30, 0.24
Month 12: 0.63, 0.59
Month 18: 0.98, 0.79
Month 24: 1.30, 1.11
### Retinal tissue and RPE cells preserved* with pegcetacoplan: Nonsubfoveal subgroup

<table>
<thead>
<tr>
<th>Pegcetacoplan monthly (n=158)</th>
<th>Pegcetacoplan EOM (n=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month intervals</td>
<td></td>
</tr>
<tr>
<td>0–6 months</td>
<td>0.30 Retinal tissue saved (mm²)</td>
</tr>
<tr>
<td></td>
<td>1500–2300 RPE cells saved</td>
</tr>
<tr>
<td>6–12 months</td>
<td>0.34 Retinal tissue saved (mm²)</td>
</tr>
<tr>
<td></td>
<td>1700–2600 RPE cells saved</td>
</tr>
<tr>
<td>12–18 months</td>
<td>0.35 Retinal tissue saved (mm²)</td>
</tr>
<tr>
<td></td>
<td>1800–2700 RPE cells saved</td>
</tr>
<tr>
<td>18–24 months</td>
<td>0.32 Retinal tissue saved (mm²)</td>
</tr>
<tr>
<td></td>
<td>1600–2500 RPE cells saved</td>
</tr>
<tr>
<td>Total over 24Mᵃ</td>
<td>1.30 Retinal tissue saved (mm²)</td>
</tr>
<tr>
<td></td>
<td>6600–10,000 RPE cells saved</td>
</tr>
</tbody>
</table>

*Estimated based on macular RPE density* range of 5082 cells/mm² to 7728 cells/mm²

**OAKS and DERBY combined**

*Numbers may differ slightly from total of 6-month intervals due to rounding.
EOM=every other month; RPE, retinal pigment epithelium.
Functional data by lesion distance from the foveal center

Post hoc subgroup analyses

- **Subgroups:** ≥250 μm and <250 μm from the foveal center

- **Data Source:** AI-based automated segmentation of RPE loss from OAKS and DERBY patients with Spectralis (Heidelberg) OCT Images (~75% total sample size)

- **Model specification and baseline covariate selection were done a priori** based on clinical rationale\(^1,2\): demographics, study eye characteristics (including foveal occupancy of regions 1–5), and fellow eye characteristics

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AI=artificial intelligence; OCT=optical coherence tomography; RPE, retinal pigment epithelium.
BCVA is correlated with the proportion of the fovea (ETDRS regions 1-5) occupied by GA lesion

- **Foveal Occupancy**: proportion of the central subfield and the inner ring of the ETDRS grid (regions 1-5) occupied by the GA lesion

- **OAKS and DERBY Baseline Data**: increasing levels of central 3 mm foveal region occupancy showed a trend toward lower BCVA scores

*Analysis only included patients with OCT images from SPECTRALIS® machines (~75% of OAKS and DERBY sample).

BCVA=best-corrected visual acuity; GA=geographic atrophy; OCT=optical coherence tomography; RPE=retinal pigment epithelium.
Pegcetacoplan was associated with slower vision loss and better quality of life in patients with lesions ≥250μm away from the foveal center.

Baseline BCVA: PEG 73 and Sham 75 (~20/32 Snellen)

BCVA change from baseline to Month 24

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Month 4</th>
<th>Month 8</th>
<th>Month 12</th>
<th>Month 16</th>
<th>Month 20</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>-1.0</td>
<td>-2.2</td>
<td>-3.0</td>
<td>-4.3</td>
<td>-5.0</td>
<td>-5.2</td>
</tr>
<tr>
<td>0.0</td>
<td>-1.4</td>
<td>-2.0</td>
<td>-3.0</td>
<td>-4.3</td>
<td>-5.0</td>
<td>-5.2</td>
</tr>
</tbody>
</table>

VFQ-25 composite baseline change from baseline to Month 24*

<table>
<thead>
<tr>
<th></th>
<th>PEG</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFQ-25</td>
<td>72.0</td>
<td>71.4</td>
</tr>
<tr>
<td>Difference (SE)</td>
<td>+4.1 (2.4)</td>
<td>+5.6 (3.2)*</td>
</tr>
</tbody>
</table>

*Adjusted difference, mean (SE)

BCVA=best-corrected visual acuity; PEG=pegcetacoplan; SE=standard error; VFQ=visual function questionnaire.
Overall trends in BCVA and VFQ-25 change over time were similar across treated and sham patients with lesions closer to foveal center (<250μm)

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### Baseline BCVA: PEG 56 and Sham 55 (~20/80 Snellen)

<table>
<thead>
<tr>
<th>Time</th>
<th>BCVA change from baseline to Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.0</td>
</tr>
<tr>
<td>Month 4</td>
<td>0.3</td>
</tr>
<tr>
<td>Month 8</td>
<td>-0.6</td>
</tr>
<tr>
<td>Month 12</td>
<td>-1.4</td>
</tr>
<tr>
<td>Month 16</td>
<td>-3.3</td>
</tr>
<tr>
<td>Month 20</td>
<td>-4.1</td>
</tr>
<tr>
<td>Month 24</td>
<td>-5.8</td>
</tr>
</tbody>
</table>

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**VFQ-25 composite change from baseline to Month 24**

<table>
<thead>
<tr>
<th>Group</th>
<th>VFQ-25 composite baseline</th>
<th>VFQ-25 composite change from baseline to Month 24*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG</td>
<td>63.8</td>
<td>-4.7</td>
</tr>
<tr>
<td>Sham</td>
<td>63.6</td>
<td>-2.4</td>
</tr>
<tr>
<td>Difference (SE)</td>
<td>-2.3 (1.0)</td>
<td></td>
</tr>
</tbody>
</table>

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*Adjusted difference, mean (SE)

BCVA=best-corrected visual acuity; PEG=pegcetacoplan; SE=standard error; VFQ=visual function questionnaire.
Over 24 months, in patients with lesions further from foveal center:

- Pegcetacoplan slowed vision loss versus sham (nearly 6 fewer letters lost)
- Pegcetacoplan-treated patients reported better quality of life than sham-treated patients (4 points higher)
  - A VFQ-25 composite difference of 4–6 points is considered clinically meaningful in neovascular AMD

Limitations

- RPE-loss data was not available for patients with Cirrus (Zeiss) OCT images
  - Baseline characteristics of patients with Spectralis and Cirrus OCT images were similar
- Post hoc analysis


AMD=age-related macular degeneration; GA=geographic atrophy; OCT=optical coherence tomography; RPE=retinal pigment epithelium; VFQ=visual function questionnaire.
Summary

• Pegcetacoplan is the first and only FDA-approved treatment for GA secondary to AMD

• Pegcetacoplan slows GA progression with both monthly and every other month dosing, with effects increasing over time
  – Treatment benefit demonstrated across all pre-specified subgroups

• In the quartile analysis, Quartile 1 (slow progressors) had a higher proportion of patients from PM and PEOM arms versus sham. Conversely, Quartile 4 (fast progressors) had a higher proportion of sham patients than PM or PEOM

• Based on the area of retinal tissue preserved, between 3500–10,000 RPE are saved with 2 years of treatment, which corresponds with a much larger number of PR cells saved.

• Pegcetacoplan demonstrated visual function and quality of life benefits vs sham in patients with lesions further from the fovea.

AMD=age-related macular degeneration; FDA=Food and Drug Administration; GA=geographic atrophy; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.