Geographic Atrophy Lesion Growth in Pegcetacoplan-treated Study Eyes Versus Untreated Fellow Eyes in Patients with Bilateral GA in the OAKS, DERBY, and FILLY Trials

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Disclosures

• Eleonora Lad has the following financial interests or relationships to disclose:
  
  • Scientific Advisor: IMI-2 Consortium, Roche, Novartis, Apellis, Allegro, Alexion, Annexon, Gemini Therapeutics, Retrotepe, Galimedix, IVERIC Bio, NGM Biopharmaceuticals, Janssen, Thea Laboratoires, LumiThera, Nanoscope Therapeutics, Perceive Biotherapeutics
  
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Summary

• In bilateral GA, growth rate of GA lesions in both eyes is highly correlated

• Therefore, analysis of study eye versus fellow eye lesion growth in patients with bilateral GA is an important internal control that reinforces and provides additional support for the biological drug effect observed in the primary analysis

• In DERBY, OAKS, and FILLY, fellow eye GA lesion growth rates were similar to those observed in natural history studies (~2 mm² per year)

• Pegcetacoplan consistently reduced GA lesion growth in treated study eyes versus untreated fellow eyes across three large, well-controlled clinical studies
Global phase 3 program: Design of studies

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

Double masked

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
- Reading speed
- NEI-VFQ-25
- FRI Index score
- Microperimetry (OAKS only) – Macular Integrity Assessment (MAIA) device

Primary Analysis: MMRM Methodology
Fixed effects:
- Treatment*, time, treatment × time interaction
- baseline GA lesion and fellow eye CNV area strata
- baseline GA lesion strata × time interaction
*Sham monthly and EOM were pooled for analysis

Month 18 Analysis conducted

Protocol study number, APL-2 303 (DERBY); NCT03525600
Protocol study number, APL-2 304 (OAKS); NCT03525613

AMD=age-related macular degeneration; BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; EOM=every other month; FRI=Functional Reading Independence; GA=geographic atrophy; LL=low luminance; MMRM=mixed-effect model for repeated measures; NEI-VFQ=National Eye Institute Visual Function Questionnaire-25.
Key inclusion and exclusion 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
  - Foveal and extrafoveal GA allowed
  - If multifocal, at least 1 focal lesion must be ≥1.25 mm² (0.5 DA)
  - Presence of perilesional hyperautofluorescence

**Key exclusion criteria**

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

Ocular history of active CNV in the fellow eye is not exclusionary

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AMD=age-related macular degeneration; BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; DA=disk area; ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; RPE=retinal pigment epithelium.
## Patient disposition at Month 18

<table>
<thead>
<tr>
<th></th>
<th>OAKS</th>
<th></th>
<th>DERBY</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PM (N=213)</td>
<td>PEOM (N=212)</td>
<td>Sham Pooled (N=212)</td>
<td>PM (N=206)</td>
<td>PEOM (N=208)</td>
</tr>
<tr>
<td><strong>Completed</strong> study</td>
<td>165 (77.5%)</td>
<td>179 (84.4%)</td>
<td>172 (81.1%)</td>
<td>167 (81.1%)</td>
<td>176 (84.6%)</td>
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<tr>
<td>through Month 18, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Discontinued</strong></td>
<td>48 (22.5%)</td>
<td>33 (15.6%)</td>
<td>40 (18.9%)</td>
<td>39 (18.9%)</td>
<td>32 (15.4%)</td>
</tr>
<tr>
<td>study prior to</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Month 18, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>**Reason for</td>
<td>Consent withdrawal</td>
<td>22 (10.3%)</td>
<td>14 (6.6%)</td>
<td>24 (11.7%)</td>
<td>13 (6.3%)</td>
</tr>
<tr>
<td>discontinuation, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>12 (5.6%)</td>
<td>7 (3.3%)</td>
<td>7 (3.3%)</td>
<td>6 (2.9%)</td>
<td>4 (1.9%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>6 (2.8%)</td>
<td>4 (1.9%)</td>
<td>3 (1.4%)</td>
<td>3 (1.5%)</td>
<td>4 (1.9%)</td>
</tr>
<tr>
<td>COVID-19 impact</td>
<td>5 (2.3%)</td>
<td>3 (1.4%)</td>
<td>11 (5.2%)</td>
<td>3 (1.5%)</td>
<td>9 (4.3%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>3 (1.4%)</td>
<td>4 (1.9%)</td>
<td>4 (1.9%)</td>
<td>1 (0.5%)</td>
<td>2 (1.0%)</td>
</tr>
</tbody>
</table>

These analyses were performed on the Month 18 intent-to-treat (ITT) population. The ITT set includes all randomized patients. N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.
## Exposure at Month 18

<table>
<thead>
<tr>
<th></th>
<th>OAKS (N=202)</th>
<th></th>
<th></th>
<th>OAKS (N=201)</th>
<th></th>
<th></th>
<th>DERBY (N=201)</th>
<th></th>
<th></th>
<th>DERBY (N=195)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PM</strong></td>
<td><strong>PEOM</strong></td>
<td><strong>Sham</strong></td>
<td><strong>PM</strong></td>
<td><strong>PEOM</strong></td>
<td><strong>Sham</strong></td>
<td></td>
<td><strong>PM</strong></td>
<td><strong>PEOM</strong></td>
<td><strong>Sham</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total number of injections received</strong></td>
<td>2991</td>
<td>1610</td>
<td>2321</td>
<td>2947</td>
<td>1553</td>
<td>2181</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Total number of missed injections</strong></td>
<td>359</td>
<td>127</td>
<td>303</td>
<td>418</td>
<td>176</td>
<td>298</td>
<td></td>
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<tr>
<td><strong>Mean number of injections/patient, n (SD)</strong></td>
<td>14.8 (4.08)</td>
<td>7.9 (1.97)</td>
<td>11.2 (4.74)</td>
<td>14.7 (4.03)</td>
<td>7.7 (1.87)</td>
<td>11.2 (4.70)</td>
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<tr>
<td><strong>Mean duration(^a) of treatment, days (SD)</strong></td>
<td>485.5 (120.49)</td>
<td>491.1 (120.20)</td>
<td>489.7 (113.78)</td>
<td>482.5 (117.63)</td>
<td>496.1 (105.89)</td>
<td>492.2 (115.21)</td>
<td></td>
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</tr>
<tr>
<td><strong>Mean compliance, %</strong></td>
<td>88.5%</td>
<td>92.4%</td>
<td>88.6%</td>
<td>87.0%</td>
<td>89.5%</td>
<td>88.8%</td>
<td></td>
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</tr>
</tbody>
</table>

The modified intent-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.

\(^a\) Duration of treatment in monthly group is (date of last injection + 30 days) – date of first injection + 1; EOM group is (date of last injection + 60 days) – date of first injection + 1. Duration of treatment is truncated to a patient’s early termination date, Month 18 cutoff date, or study completion date, as appropriate. Compliance (%) is the number of injections administered divided by the number of scheduled injections up to completion or discontinuation of study treatment × 100.

EOM=every other month; GA=geographic atrophy; N=number of patients; PEOM=pegcetacoplan EOM; PM=pegcetacoplan monthly; SD=standard deviation.
Pegcetacoplan reduced GA lesion growth vs. sham in OAKS and DERBY at Month 18

**OAKS**

*22% (monthly) reduction*  
\[ p<0.0001 \] (nominal) vs sham  

*16% (every other month) reduction*  
\[ p=0.0018 \] (nominal) vs sham

**DERBY**

*13% (monthly) reduction*  
\[ p=0.0254 \] (nominal) vs sham  

*12% (every other month) reduction*  
\[ p=0.0332 \] (nominal) vs sham

LS means estimated from a mixed-effects model for repeated measures. The modified intent-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.
Lesion growth rate is similar for both eyes in patients with bilateral GA

GA progression correlation in bilateral GA\(^1\)

![Graph showing GA progression correlation in bilateral GA](image)

Area of lesion in bilateral GA\(^2\)

![Image showing area of lesion in bilateral GA](image)

Data points indicate patients with bilateral GA. There was high correlation between eyes (\(r = 0.86; P < .001\)).

GA lesion growth is similar in patients with bilateral GA; therefore, fellow eye analyses can be an important internal control.

GA=geographic atrophy.

Analysis of fellow eye vs. study eye lesion growth

- Patients with bilateral GA were included in this analysis from DERBY and OAKS.
- In addition, for a subject to be included, the fellow eye had to meet the following criteria:
  - Absence of CNV in the medical history.
  - Baseline GA lesion size between 2.5 and 17.5 mm².
  - Presence of any pattern of hyperautofluorescence in the junctional zone of GA.
  - GA not confluent with peripapillary atrophy.
- In DERBY and OAKS, fellow eye GA lesion characteristics were similar to study eye GA lesion characteristics (e.g., majority were multifocal, majority were foveal-involving).
- In FILLY, all patients with bilateral GA were included due to sample size.
- Sham-adjusted values for the difference between fellow eye and study eye were also calculated.
  - Sham-adjusted percent difference in study eye vs. fellow eye lesion growth in pegcetacoplan-treated groups adjusts for difference in lesion growth between study eye and fellow eye in sham group.

Sham-adjusted percentage difference is derived as the difference in LS means of change from baseline between the study eye and fellow eye within the pegcetacoplan treatment groups minus the difference in LS means change from baseline between the study eye and fellow eye within the sham pooled treatment group and then divided by the change from baseline in the fellow eye within the pegcetacoplan treatment group.

CNV=choroidal neovascularization; GA=geographic atrophy; LS=least squares.
FILLY: pegcetacoplan-treated eyes demonstrated reduced lesion growth over 12 months in treated study eyes vs. untreated fellow eyes.

**18% reduced growth**

study eye vs. fellow eye
p=0.0094 (nominal)

**12% reduced growth**

study eye vs. fellow eye
p=0.0951 (nominal)

**4% faster growth**

study eye vs. fellow eye
p=0.5555 (nominal)

LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis in patients with bilateral GA with at least one post-baseline fundus autofluorescence assessment.

GA=geographic atrophy; LS=least squares; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
DERBY: pegcetacoplan-treated eyes demonstrated reduced lesion growth over 18 months in treated study eyes vs. untreated fellow eyes.

Studies

- **PM (n=87)**
  - Sham adjusted: 12% reduction vs. fellow eye; p=0.0053 (nominal)

- **PEOM (n=105)**
  - Sham adjusted: 16% reduction vs. fellow eye; p=0.0001 (nominal)
  - 12% reduced growth study eye vs. fellow eye; p=0.0053 (nominal)
  - 16% reduced growth study eye vs. fellow eye; p=0.0001 (nominal)

- **Sham (n=87, pooled)**
  - No difference (0%) study eye vs. fellow eye; p=0.9739 (nominal)
  - 16% reduced growth study eye vs. fellow eye; p<0.0001 (nominal)

LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis in patients with bilateral GA with at least one post-baseline fundus autofluorescence assessment and with fellow eyes that meet the criteria on slide 10. GA=geographic atrophy; LS=least squares; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
**OAKS**: pegcetacoplan-treated eyes demonstrated reduced lesion growth over 18 months in treated study eyes vs. untreated fellow eyes.

LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis in patients with bilateral GA with at least one post-baseline fundus autofluorescence assessment and with fellow eyes that meet the criteria on slide 10.

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

- Analysis of study versus fellow eye lesion growth in patients with bilateral GA is an important internal control to demonstrate biological drug effect
  - Fellow eye GA lesion growth rates were similar to those observed in natural history studies (~2 mm² per year)
  - The most rapid untreated fellow eye GA lesion growth was observed in the DERBY monthly pegcetacoplan arm, suggesting that patients randomized to monthly pegcetacoplan treatment in DERBY may have been predisposed to faster progression

- Pegcetacoplan consistently reduced GA lesion growth in treated study eyes versus untreated fellow eyes across three large, well-controlled clinical studies

GA=geographic atrophy