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

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30 September 2021
Retina Society 2021, Chicago, USA
Disclosures

• Dr. Heier is a consultant for 4DMT, Adverum, Aerie, Aerpio, Aldeyra, Allegro, Alzheon, Annexon, Apellis, Aprea, Asclepix, Aviceda, BVT, Dark Horse, DTx, Eloxx, Galimedix, Genentech, Graybug, Gyroscope, Iveric Bio, jCyte, Kanghong, LensGen, NGM, Novartis, Ocular Therapeutix, OcuTerra, Oxurion, Palatin, Regeneron, Regenxbio, Stealth, Thea, Version, Vinci, and Voyant.

• Dr. Heier receives research funding from: Apellis, Asclepix, Bayer, Genentech, Graybug, Gyroscope, Hemera, Iveric, Kanghong, Kodiak, NGM, Notal Vision, Novartis, Regeneron, Regenxbio, and Stealth.

• Studies funded by Apellis Pharmaceuticals
Dysregulation of the complement cascade has been implicated in GA pathogenesis

- All 3 complement pathways end in the central cleavage of C3
- Pegcetacoplan is a pegylated, highly-selective peptide that binds C3, preventing its cleavage
- Inhibition of C3 blocks steps in the complement cascade needed for opsonization, inflammation, and formation of MAC
Introduction and objective

Phase 2 FILLY Results

Change from baseline in square root GA lesion size (mm)

- **Phase 3 DERBY & OAKS objective:** to assess the efficacy and safety of multiple intravitreal injections of pegcetacoplan in patients with GA secondary to AMD

*P<0.1 was the predefined threshold for statistical significance in FILLY.
AMD=age-related macular degeneration; GA=geographic atrophy; LS=least squares; M=Month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
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

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

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

AMD=age-related macular degeneration; BCVA=best-corrected visual acuity; CNV=choroidal neovascularisation; DA=disc area; ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; RPE=retinal pigment epithelium.
Key endpoints

Primary

- Change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm²) based on FAF

Secondary (prespecified analyses to be conducted at 24 months)

- BCVA, LL-BCVA, low-luminance deficit
- Reading speed
- Microperimetry (OAKS study only*) — Macular Integrity Assessment (MAIA) device
- National Eye Institute Visual Functioning Questionnaire 25-Item Version (NEI VFQ-25)
- Functional Reading Independence Index (FRI) composite score

*Patients must meet following criteria: (a) able to detect fixation target, (b) total elapsed time to complete 68-point exam <30 min, (c) reliability test ratio <20%, (d) willing and able to undertake microperimetry in investigator’s opinion.

BCVA=best-corrected visual acuity; FAF=fundus autofluorescence; LL-BCVA=low-luminance BCVA; GA=geographic atrophy.
These analyses were performed on the modified intention-to-treat (mITT) population. The mITT population was 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; mm = millimeters; n = number of patients; NL-BCVA = normal luminance best-corrected visual acuity; PM = pegcetacoplan monthly; PEOM = pegcetacoplan every other month; ROW = rest of world; SD = standard deviation; US = United States.

### Key demographics and baseline study eye characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PM (N=202)</th>
<th>PEOM (N=205)</th>
<th>Sham Pooled (N=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>78.8 (7.24)</td>
<td>78.1 (7.74)</td>
<td>78.6 (7.26)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>125 (61.9%)</td>
<td>117 (57.1%)</td>
<td>133 (64.6%)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>77 (38.1%)</td>
<td>88 (42.9%)</td>
<td>73 (35.4%)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US, n (%)</td>
<td>147 (72.8%)</td>
<td>142 (69.3%)</td>
<td>147 (71.4%)</td>
</tr>
<tr>
<td>ROW, n (%)</td>
<td>55 (27.2%)</td>
<td>63 (30.7%)</td>
<td>59 (28.6%)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>185 (91.6%)</td>
<td>189 (92.2%)</td>
<td>187 (90.8%)</td>
</tr>
<tr>
<td>GA lesion size (mm²), mean (SD)</td>
<td>8.18 (3.893)</td>
<td>8.29 (3.904)</td>
<td>8.20 (3.722)</td>
</tr>
<tr>
<td>Square root GA lesion size (mm), mean (SD)</td>
<td>2.78 (0.682)</td>
<td>2.80 (0.674)</td>
<td>2.79 (0.649)</td>
</tr>
<tr>
<td>GA lesion size, n (%)</td>
<td>&lt;7.5 mm²</td>
<td>101 (50.0%)</td>
<td>99 (48.3%)</td>
</tr>
<tr>
<td>Extrafoveal</td>
<td>86 (42.6%)</td>
<td>74 (36.1%)</td>
<td>60 (29.1%)</td>
</tr>
<tr>
<td>Unifocal</td>
<td>59 (29.2%)</td>
<td>62 (30.2%)</td>
<td>68 (33.0%)</td>
</tr>
<tr>
<td>Intermediate/large drusen, n (%)</td>
<td>&gt;20</td>
<td>93 (46.0%)</td>
<td>104 (50.7%)</td>
</tr>
<tr>
<td>ETDRS letters, mean (SD)</td>
<td>61.0 (15.30)</td>
<td>58.2 (17.03)</td>
<td>57.5 (16.57)</td>
</tr>
</tbody>
</table>

OAKS
### Key demographics and baseline study eye characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PM (N=201)</th>
<th>PEOM (N=200)</th>
<th>Sham Pooled (N=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>78.7 (6.91)</td>
<td>79.2 (7.07)</td>
<td>78.6 (7.29)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>118 (58.7%)</td>
<td>120 (60.0%)</td>
<td>122 (62.9%)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>83 (41.3%)</td>
<td>80 (40.0%)</td>
<td>72 (37.1%)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US, n (%)</td>
<td>142 (70.6%)</td>
<td>122 (61.0%)</td>
<td>122 (62.9%)</td>
</tr>
<tr>
<td>ROW, n (%)</td>
<td>59 (29.4%)</td>
<td>78 (39.0%)</td>
<td>72 (37.1%)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>187 (93.0%)</td>
<td>185 (92.5%)</td>
<td>187 (96.4%)</td>
</tr>
<tr>
<td>GA lesion size (mm²), mean (SD)</td>
<td>8.36 (4.182)</td>
<td>8.22 (3.886)</td>
<td>8.26 (4.260)</td>
</tr>
<tr>
<td>Square root GA lesion size (mm), mean (SD)</td>
<td>2.80 (0.723)</td>
<td>2.79 (0.677)</td>
<td>2.78 (0.734)</td>
</tr>
<tr>
<td>GA lesion size, n (%)</td>
<td>&lt;7.5 mm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unifocal, n (%)</td>
<td>99 (49.3%)</td>
<td>98 (49.0%)</td>
<td>94 (48.5%)</td>
</tr>
<tr>
<td>GA lesion focality, n (%)</td>
<td>Extrafoveal</td>
<td>72 (35.8%)</td>
<td>81 (40.5%)</td>
</tr>
<tr>
<td>Intermediate/large drusen, n (%)</td>
<td>54 (26.9%)</td>
<td>53 (26.5%)</td>
<td>66 (34.0%)</td>
</tr>
<tr>
<td>NL-BCVA (ETDRS letters), mean (SD)</td>
<td>59.5 (17.40)</td>
<td>58.9 (15.97)</td>
<td>59.1 (16.85)</td>
</tr>
</tbody>
</table>

These analyses were performed on the modified intention-to-treat (mITT) population. The mITT population was 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; mm=millimeters; n=number of patients; NL-BCVA=normal luminance best-corrected visual acuity; PM=pegcetacoplan monthly; PEOM=pegcetacoplan every other month; ROW=rest of world; SD=standard deviation; US=United States.
Pegcetacoplan monthly and every other month met the primary endpoint in OAKS

LS means estimated from a mixed-effects model for repeated measures (MMRM). 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 square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Pegcetacoplan did not meet the primary endpoint in DERBY

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Pegcetacoplan reduced lesion growth in a prespecified analysis of OAKS and DERBY combined.

14% (every other month) reduction
p=0.0012 vs sham

17% (monthly) reduction
p<0.0001 vs sham

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.

GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Pegcetacoplan reduced lesion growth in patients with extrafoveal lesions in a prespecified analysis.

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis. GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Pegcetacoplan reduced lesion growth in patients with extrafoveal lesions in a prespecified combined analysis

- Pegcetacoplan reduced lesion growth by 26% (monthly) vs sham \(p<0.0001\).
- Pegcetacoplan reduced lesion growth by 23% (every other month) vs sham \(p=0.0002\).

Graph showing the LS mean change (±SE) from baseline in GA lesion (mm²) over months (M2, M4, M6, M8, M10, M12) for Sham (n=133, pooled), PEOM (n=155), and PM (n=158).

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.

GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Pegcetacoplan reduced lesion growth in patients with foveal lesions in OAKS in a prespecified analysis

**OAKS**

- Sham (n=146, pooled)
- PEOM (n=131)
- PM (n=116)

**DERBY**

- Sham (n=121, pooled)
- PEOM (n=119)
- PM (n=129)

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis. GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Pegcetacoplan reduced lesion growth in patients with foveal lesions in a prespecified combined analysis

9% (every other month) reduction
p=0.1127 vs sham

12.0% (monthly) reduction
p=0.0280 vs sham

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.

LS=least square; M=month; PEOM=PEGCETACOPLAN every other month; PM=PEGCETACOPLAN monthly; SE=standard error.
LS mean change (±SE) from baseline in GA lesion (mm²)

**OAKS**

- 13% (every other month) reduction
  - p=0.0769 vs sham
- 22% (monthly) reduction
  - p=0.0023 vs sham

**DERBY**

- 13% (every other month) reduction
  - p=0.1097 vs sham
- 19% (monthly) reduction
  - p=0.0169 vs sham

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.

GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Prespecified subgroup analysis: Rest of World sites

**OAKS**

- **25% (every other month) reduction**
  - p=0.0069 vs sham
- **21% (monthly) reduction**
  - p=0.0420 vs sham

**DERBY**

- **7% (every other month) reduction**
  - p=0.4468 vs sham
- **3% (monthly) increase**
  - p=0.7799 vs sham

Baseline M2 M4 M6 M8 M10 M12

LS mean change (±SE) from baseline in GA lesion (mm²)

Sham (n=59, pooled) PEOM (n=63) PM (n=55)

Sham (n=72, pooled) PEOM (n=78) PM (n=59)

LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.

GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Patients with bilateral GA were included in this analysis.
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

CNV=choroidal neovascularization; GA=geographic atrophy.
Pegcetacoplan reduced lesion growth in an analysis of the study eye vs untreated fellow eye, supporting primary analysis

OAKS AND DERBY

Sham pooled (n=195)

4% faster growth vs fellow eye
p = 0.2666

PEOM (n=211)

11% slower growth vs fellow eye
p = 0.0011

PM (n=177)

16% slower growth vs fellow eye
p < 0.0001

In DERBY and OAKS, study eye vs fellow eye comparison was prespecified; statistical modeling was performed post-hoc. LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis. In addition, patients must have bilateral GA and a fellow eye that meets the following key characteristics at baseline: absence of CNV in the medical history; baseline GA lesion size between 2.5 and 17.5 mm² and have at least one study eye or fellow eye at measurement at Month 6 or Month 12. In the FILLY analysis, all bilateral GA patients are included. CNV=choroidal neovascularization; GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Post-hoc covariate analysis: Background

• Question: What is the real effect size of pegcetacoplan?

• Apellis has taken a multi-pronged approach to understand inconsistent results across trials, including a significant investigation of study operations, regional differences, as well as imbalances in baseline characteristics that impact lesion growth.

• We undertook a post-hoc analysis to examine the potential contribution of baseline characteristic imbalances on the diverging results. The 8 most relevant variables related to GA were investigated for imbalance, and analyses were re-run adjusting for the imbalanced variables:

<table>
<thead>
<tr>
<th>Study eye focality</th>
<th>Study eye low luminance deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study eye lesion location</td>
<td>Region GA laterality</td>
</tr>
<tr>
<td>Study eye lesion size</td>
<td>Study eye intermediate/large drusen</td>
</tr>
<tr>
<td>Study eye pseudodrusen</td>
<td></td>
</tr>
<tr>
<td>Imbalanced in DERBY (favoring sham)</td>
<td>Imbalanced in FILLY (favoring PM)</td>
</tr>
<tr>
<td>Imbalanced in OAKS (favoring sham)</td>
<td></td>
</tr>
</tbody>
</table>

• We are presenting initial findings from this investigation.

GA=geographic atrophy; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.
Converging treatment effect of pegcetacoplan across OAKS, DERBY, in FILLY in covariate-adjusted post-hoc analysis

OAKS

- Sham (n=205, pooled)
- PEOM (n=205)
- PM (n=202)

- Baseline
- M2
- M4
- M6
- M8
- M10
- M12

- 18% (every other month) reduction
- 26% (monthly) reduction

DERBY

- Sham (n=194, pooled)
- PEOM (n=200)
- PM (n=201)

- Baseline
- M2
- M4
- M6
- M8
- M10
- M12

- 15% (every other month) reduction
- 16% (monthly) reduction

FILLY

- Sham (n=80, pooled)
- PEOM (n=78)
- PM (n=84)

- Baseline
- M2
- M4
- M6
- M8
- M10
- M12

- 18% (every other month) reduction
- 25% (monthly) reduction

LS means estimated from a mixed-effects model for repeated measures. The mITT population was used for the analysis.
SE=standard error; PM, pegcetacoplan monthly; PEOM, pegcetacoplan every other month.
Conclusions

• Pegcetacoplan monthly and every other month met the primary endpoint in OAKS
• Pegcetacoplan monthly and every other month did not meet the primary endpoint in DERBY
• Pegcetacoplan demonstrated greater efficacy in patients with extrafoveal lesions at baseline
• OAKS, DERBY, and FILLY all show consistent efficacy of pegcetacoplan in treated study eyes versus untreated fellow eyes
• In a post-hoc analysis, after correcting for disparities in baseline characteristics, OAKS, DERBY, and FILLY results are more convergent. Investigation is still ongoing
• The pegcetacoplan GA development program includes over 1,500 patients across OAKS, DERBY, and FILLY, collectively demonstrating slowing of GA progression by pegcetacoplan monthly and every other month

GA=geographic atrophy.