APL-2 (pegcetacoplan)
Geographic atrophy
Preliminary 18-month results

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The Macula Society
February 22, 2018
Financial disclosures

• Consultant – Genentech, Regeneron, Novartis/Alcon, Optos, Zeiss

• Sponsored research support – Apellis, Genentech, Regeneron, Alcon/Novartis, Clearside
The Complement Pathway and Geographic Atrophy

- **Lectin Pathway**
- **Classical Pathway**
- **Alternative Pathway**

**APL-2**

- **C3a**: Inflammation
- **C3b**: Cell removal, Antigen uptake by APCs
- **C5a**: Inflammation
- **C5b**: Cell death, secretion, lysis, or proliferation

C3, C5, C3b, C5a, C5b, MAC (Membrane Attack Complex)
FILLY - Phase 2 study of APL-2 in Geographic Atrophy

Sham injections

APL-2 0 mg

Sham group, n=81

APL-2 injections every other month

APL-2 15 mg

Active group 1, n=79

APL-2 injections every month

APL-2 15 mg

Active group 2, n=86
FILLY – timeline and endpoints

Primary efficacy endpoint is the primary registration endpoint
Change in geographic atrophy (GA) lesion size from baseline to month 12.

Primary safety endpoint
Number and severity of local and systemic treatment emergent adverse events (TEAEs).
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>APL-2 Monthly N=86</th>
<th>APL-2 Every Other Month N=79</th>
<th>Sham Pooled N=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral GA, n (%)</td>
<td>71 (85.5%)</td>
<td>64 (82.1%)</td>
<td>72 (90.0%)</td>
</tr>
<tr>
<td>History of CNV in Fellow Eye, n (%)</td>
<td>36 (41.9%)</td>
<td>28 (35.4%)</td>
<td>29 (35.8%)</td>
</tr>
<tr>
<td>GA lesion size, mean, mm² (SD)</td>
<td>8.0 (3.8)</td>
<td>8.9 (4.5)</td>
<td>8.2 (4.1)</td>
</tr>
<tr>
<td>BCVA score, mean letters (SD)</td>
<td>59.8 (15.7)</td>
<td>58.4 (16.0)</td>
<td>59.8 (17.2)</td>
</tr>
<tr>
<td>BCVA score (Snellen equivalent)</td>
<td>20/63</td>
<td>20/80</td>
<td>20/63</td>
</tr>
<tr>
<td>LL-BCVA score, mean letters (SD)</td>
<td>36.3 (16.6)</td>
<td>31.4 (17.1)</td>
<td>33.6 (17.8)</td>
</tr>
</tbody>
</table>
Primary Endpoint: GA Lesion Growth

Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model
A mixed effect model with main effects of treatment, visit and GA lesion at baseline, and interactions of treatment \( \times \) visit, visit \( \times \) baseline.
mITT = All subjects receiving at least one injection and having at least one FAF image after day 1
Primary Endpoint: GA Lesion Growth

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† p=0.008 vs Sham

+ 28.6%
Primary Endpoint: GA Lesion Growth

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<table>
<thead>
<tr>
<th>Month</th>
<th>APL-2 Monthly (n=84)</th>
<th>APL-2 Every Other Month (n=78)</th>
<th>Sham Pooled (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.25</td>
<td>0.28</td>
<td>0.25</td>
</tr>
<tr>
<td>2</td>
<td>0.28</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>6</td>
<td>0.32</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>12</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
</tr>
</tbody>
</table>

* p=0.067 vs Sham
† p=0.008 vs Sham
Post hoc analysis: greater reduction in GA lesion growth from month 6 to 12

Data from subjects with a measurable GA lesion size at both Months 6 & 12. Data as of August 24, 2017
Post hoc analysis: in bilateral GA, monthly APL-2 reduced GA growth compared to contralateral eye.

Mean (±SE) Change from Baseline in Square-root GA Lesion (mm)

APL-2 Monthly Study  Sham Study
APL-2 Monthly Fellow  Sham Fellow
(n=69)  (n=72)

Pairwise Comparison p-value
AM-Study vs. Sham-Study  0.020
AM-Study vs AM-Fellow  0.083
AEOM-Study vs Sham-Study  0.079
All other pairs (except AM-S or AEOM-S vs Sham-F)  > 0.1

mITT-Bilateral GA, Observed, ANOVA at Month 12. Data as of August 24, 2017
GA Lesion Growth to 18 Months

Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model
A mixed effect model with main effects of treatment, visit and GA lesion at baseline, and interactions of treatment × visit, visit × baseline.
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LS Mean (±SE) Change from Baseline in Square Root GA Lesion (mm)

<table>
<thead>
<tr>
<th>Month</th>
<th>APL-2 Monthly (n=84)</th>
<th>APL-2 EOM (n=78)</th>
<th>Sham Pooled (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
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<td></td>
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<td>6</td>
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<td></td>
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<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p=0.097 vs Sham
† p=0.044 vs Sham

*16.3% + 20.4%
No differences were observed in visual outcomes between groups.
## New Onset Exudation – 18 months

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects with new onset exudation in study eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham Pooled</td>
<td>1% <em>(n=1)</em></td>
</tr>
<tr>
<td>APL-2 Every Other Month</td>
<td>9% <em>(n=7)</em></td>
</tr>
<tr>
<td>APL-2 Monthly</td>
<td>21% <em>(n=18)</em></td>
</tr>
</tbody>
</table>

**Graph: All subjects**
- **Sham Pooled**
- **APL-2 Every Other Month**
- **APL-2 Monthly**
## Adverse Event Profile

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>APL-2 Monthly N=86</th>
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<th>Sham Pooled N=81</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular SAEs in study eye</strong></td>
<td>4 (4.7%)</td>
<td>2 (2.5%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td><strong>Systemic (non-ocular) SAEs</strong></td>
<td>19 (22.1%)</td>
<td>24 (30.4%)</td>
<td>23 (28.4%)</td>
</tr>
<tr>
<td><strong>Treatment related ocular AEs in the study eye</strong></td>
<td>22 (25.6%)</td>
<td>11 (13.9%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>New onset exudation</strong></td>
<td>18 (20.9%)</td>
<td>7 (8.9%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td><strong>Treatment related systemic (non-ocular) AEs</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Ocular SAEs

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<tr>
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<tr>
<td><strong>Endophthalmitis</strong></td>
<td>2 (2.3%)</td>
<td>1 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>IOP increased</strong></td>
<td>1 (1.2%)†</td>
<td>1 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Retinal detachment</strong></td>
<td>1 (1.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Visual impairment</strong></td>
<td>0</td>
<td>0</td>
<td>1 (1.2%)</td>
</tr>
</tbody>
</table>

*2 culture positive for coagulase-negative Staphylococcus. 1 culture negative in the monthly group.
†2 events in a subject
Possible explanations for APL-2 associated exudation

• APL-2 induces vascular exudation in the absence of neovascularization (VEGF-Like effect)
  • FA was not required on conversion to exudative AMD so no confirmation this was truly from CNV complex
• APL-2 induces neovascularization and exudation
• APL-2 induces exudation for pre-existing subclinical neovascularization
  • FA at baseline would have missed subclinical lesions
  • ICG angiography and OCT angiography were not performed in the study
  • Structural OCT was performed – double layer sign
Summary

• APL-2 inhibits C3 and the downstream effects of the complement cascade

• APL-2 when given monthly or every other month demonstrated statistically significant differences in GA growth over 18 months as compared to placebo patients despite no treatment for 6 months

• APL-2 slowed growth of GA independent of Complement Factor I genotype

• Upon discontinuation of APL-2 at month 12, the treatment effect declines

• The risk/benefit profile at 18 months supports the decision to move to Phase 3 testing