APL-2 (pegcetacoplan)

Geographic atrophy

Preliminary 18-month results

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

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The Complement Pathway and Geographic Atrophy

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

**APL-2**

- Inflammation
- C3a
- C3b
- C5
- C5a
- C5b
- MAC

STOP

- Cell removal, Antigen uptake by APCs
- Cell death, secretion, lysis, or proliferation

STOP

STOP

STOP
FILLY - Phase 2 study of APL-2 in Geographic Atrophy

Sham injections

APL-2 injections every other month

APL-2 injections every month

Sham group, n=81

Active group 1, n=79

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

Images taken at: 0, 2, 6, 12, 18 months

- **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 × visit, visit × baseline.

mITT = All subjects receiving at least one injection and having at least one FAF image after day 1
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LS Mean (±SE) Change from Baseline in Square Root GA Lesion (mm)

Month

APL-2 Monthly (n=84)
APL-2 Every Other Month (n=78)
Sham Pooled (n=80)

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

Least Squares Mean (±SE) Change from month 6 to 12 in Square Root GA Lesion (mm)

- Sham Pooled (n=61): 0.174
- APL-2 EOM (n=54): 0.117 (p = 0.010 vs Sham)
- APL-2 Monthly (n=58): 0.093 (p < 0.001 vs Sham)

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

![Graph showing mean (±SE) change from baseline in square-root GA lesion (mm) over months.]

- **APL-2 Monthly Study**
- **Sham Study**
- **APL-2 Monthly Fellow**
- **Sham Fellow**

Data as of August 24, 2017

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

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<table>
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<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>0.28</td>
<td>0.35</td>
<td>0.39</td>
</tr>
<tr>
<td>6</td>
<td>0.26</td>
<td>0.39</td>
<td>0.41</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>0.41</td>
<td>0.49</td>
</tr>
</tbody>
</table>

LS Mean (±SE) Change from Baseline in Square Root GA Lesion (mm)

- *p=0.097 vs Sham
- †p=0.044 vs Sham

*16.3% +20.4%
Best Corrected Visual Acuity

No differences were observed in visual outcomes between groups

Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model
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New Onset Exudation – 18 months

- Sham Pooled
- APL-2 Every Other Month
- APL-2 Monthly

1% (n=1)
9% (n=7)
21% (n=18)
## Adverse Event Profile

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

### Ocular SAEs

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