APL-2 in GA: Phase II FILLY Trial
18-Month Results

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Financial Disclosures

- Speaker for Regeneron
- Speaker for Genentech
- Speaker for Alimera Sciences
- Consultant for Regenerative Patch Technologies
- Consultant for Regeneron
- Consultant for Genentech
- Consultant for Alimera Sciences
- Consultant for Vortex Surgical
- Consultant for Notal Vision
- Research funding from Zeiss
- Research funding from Genentech
- Research funding from Regeneron
Key Takeaways

• APL-2 reduced the progression of GA secondary to AMD in the largest Phase 2 GA trial (n=246)
• Results correlated to treatment frequency with increasing effect size over time
• Further confidence in results from intra-patient control
• Upon discontinuation of APL-2, treatment effect declines
Accumulation of complement fragments in plasma and in the eyes of AMD patients


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<table>
<thead>
<tr>
<th>Complement protein</th>
<th>Units</th>
<th>Controls (Median, 95th Pctl)</th>
<th>AMD patients (Median, 95th Pctl)</th>
<th>p **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>ng/ml</td>
<td>1.18 (0.85-1.48)</td>
<td>1.12 (0.89-1.53)</td>
<td>0.85</td>
</tr>
<tr>
<td>C4</td>
<td>ng/ml</td>
<td>0.24 (0.15-0.34)</td>
<td>0.23 (0.15-0.38)</td>
<td>1.0</td>
</tr>
<tr>
<td>Factor B</td>
<td>μg/ml</td>
<td>642 (378-1554)</td>
<td>803 (497-1409)</td>
<td>0.02</td>
</tr>
<tr>
<td>Factor H</td>
<td>μg/ml</td>
<td>515 (365-711)</td>
<td>546 (396-758)</td>
<td>0.21</td>
</tr>
<tr>
<td>Factor D</td>
<td>μg/ml</td>
<td>0.95 (0.30-1.23)</td>
<td>1.26 (0.09-2.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C3a</td>
<td>ng/ml</td>
<td>14.1 (10.6-21.2)</td>
<td>15.5 (11.2-26.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>C3a</td>
<td>ng/ml</td>
<td>1.67 (0.66-3.33)</td>
<td>1.85 (0.78-6.26)</td>
<td>0.04</td>
</tr>
<tr>
<td>Bb</td>
<td>ng/ml</td>
<td>1.09 (0.60-1.71)</td>
<td>1.33 (0.09-2.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C3d</td>
<td>μg/ml</td>
<td>46.9 (32.2-68.3)</td>
<td>55.2 (35.7-94.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SC3b-5</td>
<td>ng/ml</td>
<td>1.99 (0.90-7.10)</td>
<td>10.8 (3.87-77.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

(A): C3d, (B): C3dg/C3b, (C): iC3b, in drusen, choroid, sub-RPE space

**C5 staining – “soft” drusen**

**Membrane attack complex**
The Complement Pathway and Geographic Atrophy

Lectin Pathway  Classical Pathway  Alternative Pathway

APL-2  C3  Factor D

Inflammation  C3a  STOP  C3b  Cell removal, Antigen uptake by APCs

Inflammation  C5a  STOP  C5b  MAC  Cell death, secretion, lysis or proliferation

C3

C5
FILLY - Phase 2 study of APL-2 in Geographic Atrophy

- Sham Injections: n= 81
- APL-2 injections every other month: n= 79
- APL-2 injections every month: n= 86

**APL-2 injections**
- 0 mg
- 15 mg

**APL-2**
Study Design

Eligible Patients with Geographic Atrophy*
246 subjects in 43 sites†

Single Masked

Randomized 2:2:1:1

APL-2 15 mg
Monthly
(AM)
N=86

APL-2 15 mg
Every Other Month
(AEOM)
N=79

Sham
Monthly
(SM)
N=41

Sham
Every Other Month
(SEOM)
N=40

Randomization

Treatment Period‡

Follow up

*Confirmed by the central reading center using FAF images, † Not counting the 3 satellite sites. ‡ Subjects also had a safety visit at Day 7
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).
**Key Inclusion/Exclusion Criteria**

- **Inclusion Criteria:**
  - Age ≥ 50 years
  - GA due to AMD confirmed by the central reading center using FAF images:
    - Total GA area 2.5 to 17.5 mm$^2$ (1 to 7 DA) at Screening
    - For multifocal GA, at least one lesion with ≥ 1.25 mm$^2$ (0.5 DA)
    - Completely visualized GA on the macular centered images
    - Can be measured separately from any area of peripapillary atrophy
    - Hyperautofluorescence present (any pattern)
  - BCVA (ETDRS charts) of 24 letters or better (20/320 Snellen equivalent)

- **Exclusion Criteria:**
  - GA due to causes other than AMD, or retina disease other than AMD
  - History or current evidence of neovascular AMD

  **Note:** No exclusion criteria associated with the fellow eye
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sham injections N=81</th>
<th>APL-2 every other month N=79</th>
<th>APL-2 monthly N=86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral GA, n (%)</td>
<td>72 (90.0%)</td>
<td>64 (82.1%)</td>
<td>71 (85.5%)</td>
</tr>
<tr>
<td>History of CNV in Fellow Eye, n (%)</td>
<td>29 (35.8%)</td>
<td>28 (35.4%)</td>
<td>36 (41.9%)</td>
</tr>
<tr>
<td>GA lesion size, mean, mm² (SD)</td>
<td>8.2 (4.1)</td>
<td>8.9 (4.5)</td>
<td>8.0 (3.8)</td>
</tr>
<tr>
<td>BCVA score, mean letters (SD)</td>
<td>59.8 (17.2)</td>
<td>58.4 (16.0)</td>
<td>59.8 (15.7)</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>33.6 (17.8)</td>
<td>31.4 (17.1)</td>
<td>36.3 (16.6)</td>
</tr>
</tbody>
</table>

Groups were well balanced as to age, gender and race
APL-2 slows GA growth at 12 months (square root)

- sham injections
- APL-2 every other month
- APL-2 monthly

Change from baseline in square root GA lesion growth (mm):
- 2 months: 0.25
- 6 months: 0.28
- 12 months: 0.35

20% lesion growth difference p=0.067 vs Sham
29% lesion growth difference p=0.008 vs Sham

Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model
Lesion growth by six-month periods (square root) – 12 months

Sham injections

- 0-6 months
- 6-12 months

APL-2 injections every other month

- 0-6 months
- 6-12 months

APL-2 injections every month

- 0-6 months
- 6-12 months

Data from subjects with a measurable GA lesion size at both Months 6 & 12

33% lesion growth difference vs sham p=0.01

47% lesion growth difference vs sham p < 0.001
FILLY sham group behaved consistently with recent publication.

Holz, F.G., et al. Efficacy and Safety of Lampalizumab for Geographic Atrophy Due to Age-Related Macular Degeneration: Chroma and Spectri Phase 3 Randomized Clinical Trials. JAMA Ophthalmol, 2018

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sham</th>
<th>Lampalizumab, 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in square root of GA area at 48 wk, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted mean (SE)</td>
<td>0.342 (0.007)</td>
<td>0.349 (0.007)</td>
</tr>
<tr>
<td>Difference in means (vs sham pooled)</td>
<td>0.006</td>
<td>0.010</td>
</tr>
</tbody>
</table>
After cessation of treatment at 12 months, GA growth resumes but treatment effect is maintained through 18 months (square root).

**Modified Intent to Treat population (mITT): Observed, Mixed-Effect Model**

- **16% lesion growth difference**
  - p=0.097 vs Sham
  - Change from baseline in square root GA lesion growth (mm): 0.49

- **20% lesion growth difference**
  - p=0.044 vs Sham
  - Change from baseline in square root GA lesion growth (mm): 0.41
Lesion growth by six-month periods (*square root*) – **18 months**

**Sham injections**

- **0-6 months**
- **6-12 months**
- **12-18 months**

**APL-2 injections every other month**

- **0-6 months**
- **6-12 months**
- **12-18 months**

**APL-2 injections every month**

- **0-6 months**
- **6-12 months**
- **12-18 months**

Data from subjects with a measurable GA lesion size at Months 6 & 12 & 18

- **9% lesion growth difference** vs sham *p* > 0.5
- **12% lesion growth difference** vs sham *p* = 0.47

*Apellis*
GA growth comparison: fellow eye vs study eye post hoc analysis

**Sham Injections**
n= 72

**APL-2 injections every other month**
n= 63

**APL-2 injections every month**
n= 69

Includes patients from the Bilateral GA Population
Best-corrected Visual Acuity

No differences were observed in visual outcomes between groups

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
Adverse Event Profile

<table>
<thead>
<tr>
<th>Adverse Event n (%) of subjects with events</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>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>Treatment related systemic (non-ocular) AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ocular SAEs</th>
<th>APL-2 Monthly N=86</th>
<th>APL-2 EOM N=79</th>
<th>Sham Pooled N=81</th>
</tr>
</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
## New onset exudation – 18 months

<table>
<thead>
<tr>
<th>Group</th>
<th>APL-2 Monthly</th>
<th>APL-2 EOM</th>
<th>Sham Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>n = 86</td>
<td>n = 79</td>
<td>n = 81</td>
</tr>
<tr>
<td>Subjects with wAMD in Study eye (%)</td>
<td>18 (20.9%)</td>
<td>7 (8.9%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>With History of CNV in Fellow Eye</td>
<td>n = 36</td>
<td>n = 28</td>
<td>n = 29</td>
</tr>
<tr>
<td>Subjects with wAMD in Study eye (%)</td>
<td>13 (36.1%)</td>
<td>5 (17.9%)</td>
<td>0</td>
</tr>
<tr>
<td>No CNV History in Fellow Eye</td>
<td>n = 50</td>
<td>n = 51</td>
<td>n = 52</td>
</tr>
<tr>
<td>Subjects with wAMD in Study eye (%)</td>
<td>5 (10.0%)</td>
<td>2 (3.9%)</td>
<td>1 (1.9%)</td>
</tr>
</tbody>
</table>
New onset exudation

- Subjects that developed exudation had minor loss of vision and were treated with anti-VEGF
- 6 patients developed wet AMD in the 12-18 month non-treatment period (5/6 had fellow eye wet AMD)
Key Takeaways

• APL-2 reduced the progression of GA secondary to AMD in the largest Phase 2 GA trial (n=246)

• Results correlated to treatment frequency with increasing effect size over time

• Further confidence in results from intra-patient control

• Upon discontinuation of APL-2, treatment effect declines