APL-2, a Complement C3 Inhibitor, Slows the Growth of Geographic Atrophy Secondary to AMD: 18-Month Results
Financial Disclosures

• PLEASE ADD
The Complement System and Geographic Atrophy

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

- **APL-2**
- **Factor D**

Inflammation

- **C3a**
- **C3b**

- **Cell removal, Antigen uptake by APCs**

- **Cell death, secretion, lysis or proliferation**

**Factors**

- C3
- C5
- C3a
- C3b
- C5a
- C5b
- MAC
- C3a
- C3b
- C5
- C5a
- C5b
- MAC
- C3a
- C3b
- C5
- C5a
- C5b
- MAC

3
Phase 2 Study Design

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

Randomized 2:2:1:1

Single Masked

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

APL-2 15 mg Every Other Month  
(EOM)  
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.
**Endpoints**

**Primary efficacy endpoint**
Change in square root geographic atrophy lesion size from baseline to month 12

**Primary safety endpoint**
Number and severity of local and systemic treatment emergent adverse events
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)
    ▪ Can be measured separately from any area of peripapillary atrophy
    ▪ Perilesional 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 EOM 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>
APL-2 Slows GA Growth at 12 Months (square root)

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

Sham Injections

APL-2 EOM

APL-2 Monthly

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

20% lesion growth difference p=0.067 vs Sham

29% lesion growth difference p=0.008 vs Sham
## Sensitivity Analysis

<table>
<thead>
<tr>
<th>Population</th>
<th>Sham Pooled</th>
<th>APL-2 EOM</th>
<th>APL-2 Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT Population (primary endpoint)</td>
<td>n*</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>LS Mean (SE)</td>
<td>0.35 (0.025)</td>
<td>0.28 (0.026)</td>
<td>0.25 (0.025)</td>
</tr>
<tr>
<td>Reduction vs Sham</td>
<td>20%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>p-value (vs Sham)</td>
<td>0.067</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Per protocol Population</td>
<td>n*</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>LS Mean (SE)</td>
<td>0.35 (0.026)</td>
<td>0.28 (0.027)</td>
<td>0.26 (0.027)</td>
</tr>
<tr>
<td>Reduction vs Sham</td>
<td>20%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>p-value (vs Sham)</td>
<td>0.05</td>
<td>0.019</td>
<td></td>
</tr>
</tbody>
</table>

* Number of subjects who contributed to the analysis
Lesion Growth by Six-month Periods (square root) – 12 months

Sham Injections

APL-2 EOM

APL-2 Monthly

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
Change from baseline in square root of GA area at 48 wk, mm in the Phase 3 Lampalizumab (Chroma and Spectri)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sham</th>
<th>Lampalizumab, 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled (n=598)</td>
<td>q4w (n=596)</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>

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
After cessation of treatment at 12 months, GA growth resumes but treatment effect is maintained through 18 months (square root).

**Sham Injections**

**APL-2 EOM**

**APL-2 Monthly**

<table>
<thead>
<tr>
<th>Time</th>
<th>Sham Injections</th>
<th>APL-2 EOM</th>
<th>APL-2 Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>0.49</td>
<td>0.41</td>
<td>0.39</td>
</tr>
<tr>
<td>6 months</td>
<td>0.41</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>0.39</td>
<td>0.39</td>
<td>0.39</td>
</tr>
<tr>
<td>18 months</td>
<td>0.39</td>
<td>0.39</td>
<td>0.39</td>
</tr>
</tbody>
</table>

16% lesion growth difference vs Sham: p=0.097

20% lesion growth difference vs Sham: p=0.044
Lesion Growth by Six-month Periods (*square root*) – 18 Months

Data from subjects with a measurable GA lesion size at Months 6 & 12 & 18
GA Growth Comparison: Fellow Eye vs Study Eye

*post hoc analysis*

- **Sham Injections**
  - n= 72

- **APL-2 EOM**
  - n= 63
  - 10% Difference
  - p > 0.1

- **APL-2 Monthly**
  - n= 69
  - 23% Difference
  - p = 0.083

Includes patients from the Bilateral GA Population
Changes in 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 x visit, visit x 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</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>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 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 AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Ocular SAEs

<table>
<thead>
<tr>
<th></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></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 exudative AMD 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 exudative AMD 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 exudative AMD in Study eye(%)</td>
<td>5 (10.0%)</td>
<td>2 (3.9%)</td>
<td>1 (1.9%)</td>
</tr>
</tbody>
</table>

- The majority of patients that developed exudative AMD had minor loss of vision and were treated with anti-VEGF therapy
- Six patients developed exudative AMD in the 12-18 months non-treatment period (5/6 had fellow eye with history of CNV)
• 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 evidence from intra-patient control

• Upon discontinuation of APL-2, treatment effect declined

• Apellis announced first patient enrolled in the global Phase 3 study