APL-2 Treatment For Geographic Atrophy: Long-term Results

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Financial Disclosures

Please add
• Patients with complement-mediated systemic (renal) diseases have macular drusen, and drusen are a hallmark of AMD

• Abnormal systemic levels of activated complement products in AMD patients documented, and complement proteins deposited in drusen, Bruch’s membrane, and the inner choroid in AMD eyes

• Genetics strongly supports an important role for complement in AMD
The Complement Pathway

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

**C3**
- **C3a** → Inflammation
- **C3b** → Cell removal, Antigen uptake by APCs

**C5**
- **C5a** → Inflammation
- **C5b → MAC** → Cell death, secretion, lysis, or proliferation
AMD Clinical Trials with Complement Inhibitors

• Anti-Factor D Fab (intravitreal)
  - Lampalizumab: Genentech/Roche

• Anti-C5 drugs
  - Anti-C5 monoclonal antibodies:
    - LFG316 ± Anti-Properdin: Novartis (intravitreal)
    - Eculizumab: Alexion (intravenous)
  - Anti-C5 aptamer (Zimura): Ophthotech (intravitreal)

• Prevent membrane attack complex
  - AAV gene therapy delivers sCD59 (HMR59): Hemera (intravitreal)

• Anti-C3 cyclic peptide (intravitreal)
  - APL-2: Apellis
Cell death, secretion, lysis, or proliferation

Inflammation

Lectin Pathway

Classical Pathway

Alternative Pathway

C3

C3a

C3b

Cell removal, Antigen uptake by APCs

C5

C5a

C5b

MAC

Cell death, secretion, lysis, or proliferation

Most of the complement pathway remains intact

The Complement Pathway and Factor D Inhibition
The Complement Pathway and C5 Inhibition

C3, C3a, and C3b are unaffected

Cell removal, Antigen uptake by APCs

Cell death, secretion, lysis, or proliferation

Lectin Pathway
Classical Pathway
Alternative Pathway
Cell death, secretion, lysis, or proliferation

The Complement Pathway and MAC Inhibition

C3, C3a, C3b, C5, C5a, and C5b are unaffected

C3, C3a, C3b, C5, C5a, and C5b are unaffected
The Complement Pathway and C3 Inhibition

Lectin Pathway → Classical Pathway → Alternative Pathway

Complete Inhibition of the Complement Pathway

APL-2

Inflammation → C3a → C3b → C5 → C5a → C5b

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

Inflammation
Phase 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
AM (n=86)
D0 M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12

AEOM (n=79)
D0 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12

SM (n=41)
D0 M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12

SEOM (n=40)
D0 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12

Follow up
M15 M18 M15 M18 M15 M18

*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
Change in square root 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 mm² (1 to 7 DA) at Screening
  - For multifocal GA, at least one lesion with ≥ 1.25 mm² (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

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

- Sham Injections
- APL-2 EOM 20% lesion growth difference p=0.067 vs Sham
- APL-2 Monthly 29% lesion growth difference p=0.008 vs Sham

2 months  | 6 months  | 12 months
0.25      | 0.28      | 0.35
0.3       | 0.25      | 0.35
0.4       | 0.25      | 0.35
0.5       | 0.25      | 0.35

Injections
APL-2 EOM
APL-2 Monthly
### 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><strong>mITT Population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(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><strong>Per protocol Population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n*</td>
<td>73</td>
<td>71</td>
<td>66</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

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

Sham Injections

APL-2 EOM

APL-2 Monthly

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

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

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sham Pooled (n=598)</th>
<th>Lampalizumab, 10 mg q4w (n=596)</th>
<th>Lampalizumab, 10 mg q6w (n=603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted mean (SE)</td>
<td>0.342 (0.007)</td>
<td>0.349 (0.007)</td>
<td>0.352 (0.007)</td>
</tr>
<tr>
<td>Difference in means (vs sham pooled)</td>
<td>0.006</td>
<td>0.010</td>
<td></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
GA Growth Comparison: Fellow Eye vs Study Eye

*post hoc analysis*

Includes patients from the Bilateral GA Population
Benefit of APL-2 was Independent of Baseline GA Lesion Size
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

APL-2 EOM
16% lesion growth difference
p=0.097 vs Sham

APL-2 Monthly
20% lesion growth difference
p=0.044 vs Sham
Lesion Growth by Six-month Periods (*square root*) – 18 Months

Sham Injections

- 0-6 months: 0.1
- 6-12 months: 0.1
- 12-18 months: 0.1

APL-2 EOM

- 0-6 months: 0.05
- 6-12 months: 0.05
- 12-18 months: 0.05

APL-2 Monthly

- 0-6 months: 0.1
- 6-12 months: 0.1
- 12-18 months: 0.1

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

### Adverse Event n (%) of subjects with events

<table>
<thead>
<tr>
<th>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><strong>Ocular SAEs in study eye</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td></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></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 (25.6%)</td>
<td>11 (13.9%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Treatment related systemic (non-ocular) AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Ocular SAEs</strong></td>
<td>APL-2 Monthly N=86</td>
<td>APL-2 EOM N=79</td>
<td>Sham Pooled N=81</td>
</tr>
<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
Majority of patients that developed exudation had minor loss of vision and were treated with anti-VEGF therapy (avastin, ranibizumab or aflibercept).

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 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

Global Phase 3 study initiated